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The United States-Japan Cooperative Cancer Research Program

ORIGINAL

PROGRESS REPORT

April 1979 through March 1980

COMPLETED
122

The National Cancer Institute, and
Japan Society for the Promotion of Science

The United States-Japan
Cooperative Cancer Research
Program

PROGRESS REPORT

April 1979 through March 1980

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Japan Society for the Promotion of Science

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PREFACE

This report summarizes activities of the United States-Japan Cooperative Cancer Research Program for Japanese Fiscal Year 1979, the period between April 1, 1979 and March 31, 1980.

Following the very successful conclusion of the first five-year period, the US-Japan Cooperative Cancer Research Program entered on the second five-year period in April 1979, with the substantial restructuring of the Program intended for greater flexibility in operation to meet the needs of the changing interests and new research areas emerging in the recent progress of cancer research. The structure and objectives of the Second Five-Year Plan are explained in detail on pages 93-95 of this report.

The most important modification is the consolidation of the previous eleven areas of cooperation into four major areas, namely, 1) Etiology, 2) Biology and Diagnosis, 3) Treatment, and 4) Interdisciplinary Program and Coordination. The Interdisciplinary Program and Coordination Area is intended to serve the functions of general coordination of other three areas, consideration of new programs of scientific merit, facilitation of interdisciplinary programs including those on organ sites, and sponsoring of interdisciplinary meetings.

Each area of cooperation has two Program Coordinators, one appointed by each implementing agency. They are assisted by a number of Principal Advisors of their choice in planning and carrying out program activities in their own areas. A list of US/Japan Coordinators and Principal Advisors for 1979-80 appears on pages 110-112.

A number of areas of special interest were also identified for each major program area so as to indicate priority in the implementation of cooperative activities between the two countries, with the understanding that they may change during the course of five years, depending upon scientific opportunity and new knowledge. They are as follows:

I. Etiology
   - Epidemiology
   - Chemical and Radiation Carcinogenesis
   - Viral Carcinogenesis
   - Genetics

II. Biology and Diagnosis
   - Cellular and Molecular Biology
   - Immunology
   - Diagnosis

III. Treatment
   - Chemotherapy
   - Radiation Oncology
   - Immunotherapy
   - Clinical Trials

IV. Interdisciplinary Program and Coordination
   - Overall Coordination of Above Three Areas
   - Consideration of New Programs or Areas of Special Interest
   - Sponsoring of Interdisciplinary Sessions
   - Organ Sites

In place of the previous Joint Annual Meeting, where all the coordinators of the eleven areas of cooperation participated, a new Joint

Steering Committee consisting of the Program Coordinators of the four major areas and the representatives of the implementing agencies meets once every year to discuss policy matters, annual program activities to be supported, coordination among the program areas, evaluation and reporting, etc. The First new Joint Steering Committee Meeting was held in San Francisco on May 24-25, 1979. A record of the meeting is included as Appendix.

During the first year of the second five-year period, 10 seminars were held, 13 American and 11 Japanese scientists were exchanged and 2 materials were exchanged. The breakdown by areas is shown in the following table.

Area	Seminar	Exchange of Scientists		Exchange of Materials
		From U.S.	From Japan	
Etiology	2	5	6	1
Biology & Diagnosis	3	0	3	1
Treatment	3	3	1	0
Interdisciplinary Program and Coordination	2	5	1	0
Total	10	13	11	2

The implementing agencies are most appreciative of the enthusiastic and unselfish devotion that the Program Coordinators and Principal Advisors demonstrated to the successful implementation of the program. It is our sincere hope that the second five-year program will prove even more successful and fruitful than the first five-year program through an increasing interest and participation of cancer researchers of the two countries in this cooperative program.

Robert R. Omata, Ph.D.
Executive Secretary
U.S.-Japan Cooperative
Cancer Research Program
Office of International Affairs
National Cancer Institute

Kichimasa Soda
Head, Program Department
Japan Society for the Promotion of Science

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I. ETIOLOGY AREA

I. ETIOLOGY AREA

Program Coordinators: Dr. I. Bernard Weinstein, U.S.A.
Dr. Takashi Sugimura, Japan

Principal Advisors:
U.S.A.: Dr. Thomas L. Benjamin
Dr. Hidesaburo Hanafusa
Dr. Warren Nichols
Dr. Robert Miller
Japan: Dr. Shozo Takayama
Dr. Hiroto Shimojo
Dr. Susumu Nishimura
Dr. Takeshi Hirayama

1. ADMINISTRATIVE REPORT

A. Seminars

1) Seminar on "Gastrointestinal Tract Cancer" (Also see p. 5, 9)
Honolulu, Hawaii, March 3 - 6, 1980
Organizers: Dr. J. H. Weisburger, Dr. R. Bruce, Dr. T. Hirayama, Dr. S. Takayama
Participants: 13 from U.S.A.; 1 from Canada; 14 from Japan

2) Seminar on "Molecular Mechanism of DNA Synthesis in Cancer Cells" (Also see p. 6, 14)
Tokyo, Japan, March 6 - 8, 1980
Organizers: Dr. D. Korn, Dr. K. Koike
Participants: 6 from U.S.A.; 10 from Japan

B. Exchange of Scientists

1) Dr. Masakazu Hatanaka, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Md. (Also see p. 18)
Dates: from September 10 to October 20, 1979
Host scientist: Dr. Tsutomu Sugahara, Department of Experimental Radiology, Faculty of Medicine, Kyoto University, Kyoto
Subject: Chromosomal aberration and sister chromatid exchanges induction by carcinogens in the Indian muntjac cells.

2) Dr. Neil E. Spingarn, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, N. Y. (Also see p. 19)
Dates: from October 3 to December 13, 1979
Host scientist: Dr. Taijiro Matsushima, Department of Molecular Oncology, Institute of Medical Science, Tokyo University, Tokyo
Subject: Purification and identification of mutagens in cooked meats and fish.

3) Ms. Lynne A. Haroun, Staff Research Associate, Department of Biochemistry, University of California, Berkeley, Calif. (Also see p. 19)

Dates: from November 1, 1979 to January 31, 1980

Host scientists: Dr. Taijiro Matsushima, Department of Molecular Oncology, Institute of Medical Science, Tokyo University, Tokyo
Dr. Takashi Sugimura, Biochemistry Division, National Cancer Center Research Institute, Tokyo

Subjects: (a) The testing of polychlorinated hydrocarbons in the *Salmonella* assay: Activation by house fly S9.
(b) The mutagenicity of edible seaweeds.

4) Dr. Arthur Weissbach, Department of Cell Biology, Roche Institute of Molecular Biology, Nutley, N. J. (Also see p. 22)

Dates: from February 27 to March 10, 1980

Host scientist: Dr. Katsuro Koike, Cancer Institute, Japanese Foundation for Cancer Research, Tokyo

5) Dr. David Korn, Laboratory of Experimental Oncology, Department of Pathology, Stanford University, School of Medicine, Stanford, Calif. (Also see p. 23)

Dates: from February 29 to March 11, 1980

Host scientists: Dr. Katsuro Koike, Cancer Institute, Japanese Foundation for Cancer Research, Tokyo
Dr. Akio Matsukage, Laboratory of Biochemistry, Aichi Cancer Center Research Institute, Nagoya
Dr. Takeshi Seno, Saitama Cancer Center Research Institute, Saitama

6) Dr. Takeshi Hirayama, Epidemiology Division, National Cancer Center Research Institute, Tokyo (Also see p. 23)

Dates: from August 5 to August 25, 1979

Host scientist: Dr. Robert W. Miller, Chief, Clinical Epidemiology, National Cancer Institute, Bethesda, Md.

Subject: Epidemiology, Prevention Oncology.

7) Dr. Kazuo Umezawa, Department of Molecular Oncology, Institute of Medical Science, Tokyo University, Tokyo (Also see p. 24)

Dates: from August 18 to October 20, 1979

Host scientist: Dr. I. Bernard Weinstein, Professor of Medicine and Environmental Sciences, Institute of Cancer Research, College of Physicians and Surgeons of Columbia University, New York

Subject: Inhibition of cellular binding of epidermal growth factor by Staphylococcal delta-hemolysin and inhibition of cellular epidermal growth factor binding by phorbol esters in primary culture cells.

8) Dr. Norio Matsukura, Biochemistry Division, National Cancer Center Research Institute, Tokyo (Also see p. 25)

Dates: from September 1 to September 24, 1979

Host scientists: Dr. Harold L. Stewart, Scientist Emeritus, Registry of Experimental Cancers, Division of Cancer Cause and Prevention, National Cancer Institute, Bethesda, Md.

Dr. Grant N. Stemmerman, Director of Laboratories
The Japan-Hawaii Cancer Study, Kuakini Medical Center,
347 North Kuakini Street, Honolulu, Hawaii

Subject: Biochemical and pathological studies in intestinal metaplasia.

9) Dr. Hiroyuki Shimizu, Epidemiology Division, Aichi Cancer Center Research Institute, Nagoya (Also see p. 27)

Dates: from October 1, 1979 to September 30, 1980

Host scientist: Dr. Brian E. Henderson, Department of Community and Family Medicine, School of Medicine, University of Southern California, Los Angeles, Calif.

Subject: Epidemiological study on environmental factors of lung cancer. Epidemiological study on metabolic and endocrinological characteristics of prostate cancer.

10) Dr. Kazukiyo Onodera, Institute for Virus Research, Kyoto University Kyoto (Also see p. 27)

Dates: from November 19, 1979 to January 17, 1980

Host scientists: Dr. Howard Green, Massachusetts Institute of Technology
Dr. L. M. Baker, Center for Cancer Research, M.I.T.
Dr. P. W. Robbins, Center for Cancer Research, M.I.T.

Subject: Biochemical characterization of Tunicamycin resistant mutant of cancer cells.

11) Dr. Yoshiyuki Kuchino, Biology Division, National Cancer Center Research Institute, Tokyo (Also see p. 28)

Dates: from March 3 to March 31, 1980

Host scientists: Dr. Ernest Borek, Professor, University of Colorado Medical Center, Denver, Colo.
Dr. Dezider Grunberger, Institute of Cancer Research, Columbia University, New York

Subject: Study on the function of tumor specific tRNA.

C. Exchange of Materials

5 gm each of Glu-P-1 (2-amino-6-methyldipyrido [1,2-a: 3',2'-d] imidazole) and Glu-P-2 (2-amino-dipyrido [1,2-a:3",2'-d] imidazole) were sent from Japan to the U.S. to be used by American scientists. Dr. Takeo Kakunaga, National Cancer Institute, NIH, will handle the distribution of these materials to qualified scientists. Both compounds are potent mutagens isolated from pyrolysis of glutamic acid. Arrangements are being made to share with U.S. scientists some novel deoxynucleoside triphosphate analogues synthesized by Dr. Mineo Saneyoshi for research on the mechanism of DNA replication in normal and cancer cells.

2. SUMMARY OF ACTIVITIES

The year April 1, 1979 to March 31, 1980 constitutes the first year of the second Five-Year Program of the U.S.-Japan Cooperative Cancer Research Program. The major objective of the Etiology Area of this Program is to identify carcinogenic factors and clarify mechanisms of carcinogenesis with a view to providing a fundamental basis for understanding the causation of human cancer.

The etiology area includes four sub-areas, namely; Epidemiology, Chemical Carcinogenesis, Viral Carcinogenesis and Genetics. These four areas are closely inter-related and the seminars held during the past year reflect this fact. For example, the seminar entitled "Gastrointestinal Tract Cancer" held in Honolulu in March, 1980 brought together scientists from different disciplines, including epidemiology, pathology, and biochemistry. The discussions focused in two major gastrointestinal cancers - colon and stomach, which are prevalent in the U.S. and Japan, respectively. These geographic differences in incidence provided a useful contrast for discussions on etiology, the possible roles of initiators and promoters, precancerous lesions, and preventive studies.

Progress in our understanding of the etiology of cancer is closely coupled to our understanding of the normal mechanisms that control cellular growth and differentiation. For this reason, a seminar titled "Molecular Mechanisms of DNA Synthesis in Cancer Cells" was held in March, 1980 in Tokyo. This conference provided an extremely fruitful exchange of information between U.S. and Japanese scientists of new information in this important and rapidly moving field of basic research.

More detailed reports of these two conferences are given in pp. 5-8.

Detailed reports of the progress submitted by the eleven individual Scientist Exchanges are given in pp. 18-29. All of these were highly successful. As examples, brief descriptions of two Scientist Exchanges are given in this section. The visit of Dr. N. E. Spingarn to the laboratory of Dr. T. Matsushima, University of Tokyo, was extremely effective. It resulted in rapid progress in identifying new mutagens found in broiled fish and fried hamburger. The complete chemical structures of these compounds is currently being elucidated and the results will soon be available. The results of these studies will be published as a collaborative effort from the National Cancer Center Research Institute in Japan and the American Health Foundation.

The visit of Dr. Kazuo Umezawa to Columbia University led to rapid progress in at least three areas related to the molecular mechanism of action of tumor promoters, especially at the level of cellular membranes. It was found that Staphylococcal delta hemolysin, an amphipathic polypeptide, inhibits the binding to cellular receptors of epidermal growth factor (EGF); this compound also exerted other effects on cell membranes similar to the phorbol ester tumor promoters.

In a second set of studies, evidence was obtained that the specificity of cell receptor responses to a series of phorbol ester compounds is different in rodent cells than in human cells. Dr. Umezawa's visit

also stimulated a collaborative study among Drs. Umezawa, I. B. Weinstein and T. Sugimura on the membrane effects of teleocidin, a very potent and novel type of tumor promoter recently discovered in Japan. These collaborative studies are continuing and will shortly be submitted for publication. Although it has quite a different chemical structure, teleocidin is as active as the highly potent tumor promoter, 12-O-tetradecanoyl-phorbol-13 acetate (TPA). These collaborative studies indicate that teleocidin and TPA may act on the same cell surface receptors, despite the fact that these compounds have quite different chemical receptors.

3. REPORTS ON SEMINARS

1) Seminar on "Gastrointestinal Tract Cancer"

U.S.-Japan Cooperative Workshop on "The Etiology of Stomach and Colon Cancer" was held at the East-West Center, Honolulu, Hawaii on March 3 through March 6, 1980. Organizers were Dr. W. Robert Bruce, the Ontario Cancer Institute, the Princess Margaret Hospital, Toronto and Dr. John H. Weisburger, Naylor Dana Institute for Disease Prevention, American Health Foundation, New York (US side), and Dr. Takeshi Hirayama, Epidemiology Division, National Cancer Center Research Institute, Tokyo and Dr. Shozo Takayama, Experimental Pathology Division, Cancer Institute, Tokyo (Japan side). There were 28 speakers, 14 from USA and 14 from Japan. The agenda of the workshop and the names of participants are shown on pp. 9-13.

Three features of the workshop were (1) multidisciplinary search for the etiology of stomach and colon cancer (2) comparative oncology of the colon and stomach and (3) comprehensive search for carcinogens, promoters and inhibitors of these two major types of cancer. Efforts were focussed on collation and integration of available knowledge, concepts and methods in different fields of etiological research on stomach cancer and rectal-colon cancer.

During the meeting, the following topics were discussed. In epidemiology, probable and possible risk factors of stomach and colon cancer were reviewed. The importance of further studies on Japanese migrants to Hawaii was stressed. A need for retesting the hypothesis that meat consumption plays a role in colon cancer was stressed by Dr. T. Hirayama, based on prospective cohort studies in Japan and by Dr. G. Stemmerman, based on retrospective cohort studies in Hawaii. Dr. S. Tominaga classified known risk factors into seven categories according to their enhancing or supressing effect on either stomach or colon cancer, or both. Such classification was felt to be of practical importance and epidemiological research should be carried out in a comparative way in order to find out common inhibitory factors. In pathology, precursor lesions of both cancers were reviewed in detail. Biochemical and biological (e.g. bacteria flora) changes that accompany these lesions were introduced. The importance and limitations of experimental models in understanding the mechanism of carcinogenesis and also in searching for intervention measures were also discussed. The discussion on high risk groups was focussed on genetic factors with special reference to

familial polyposis and colon cancer in relation to multi hit theories. Possible carcinogens, promoters, and inhibitors for stomach cancer and colon-rectum cancer were reviewed. The significance and methods of detection of recal, local, and dietary mutagens were discussed. Recent developments in the search for promoters were reviewed by Dr. T. Sugimura and possible organ-specific promoters in humans were listed (e.g. salt in the stomach). Dr. R. Bruce emphasized a need for intervention studies using vitamin A, C, and E. Preliminary results of an intervention trial of these vitamins on chronic gastric lesions were presented by Dr. P. Correa.

In conclusion, participants from both the U.S.A. and Japan found the meeting extremely useful. The discussions were informative and generated new ideas and approaches in many of the topics presented.

The original purpose of multidisciplinary discussions on the etiology of colon and stomach cancer was achieved. Participants expressed a need for cooperative research by experts in different fields. As to the comparative oncology of colon and stomach, certain priority areas were stressed, e.g. genetic influences on the occurrence of precursor lesions or other predisposing conditions which have been well studied in colon cancer but less so in stomach cancer. With regard to comprehensive discussions on possible carcinogens, initiators, promoters, and inhibitors, the need for a multidisciplinary approach was stressed by Dr. T. Sugimura.

The meeting was quite valuable and instructive to several younger research scientists who attended the workshop. The participation of young promising researchers should be encouraged in selecting participants for future U.S.-Japan Cancer Conferences in order to encourage new ideas and approaches.

2) Seminar on "Molecular Mechanisms of DNA Synthesis in Cancer Cells"

The conference on "Molecular Mechanisms of DNA Synthesis in Cancer Cells" was held in Tokyo, Japan, March 6 - 8, 1980 under the sponsorship of this program. The meeting was organized by Dr. David Korn of the Department of Pathology, Stanford University, School of Medicine, Stanford and Dr. Katsuro Koike of the Department of Biochemistry, Cancer Institute, Tokyo. There were 16 speakers, 6 from the U.S.A. and 10 from Japan. The total number of participants was 26, including observers. The names of the speakers and the program of the meeting are shown on pp. 14-17.

A problem that is fundamental to understanding the proliferation of cancer cells is the molecular mechanism of DNA replication. This mechanism must be clarified in order to elucidate the nature of abnormal growth of cancer cells, and to develop approaches to specifically prevent the growth of tumor cells. The mechanism of DNA synthesis in mammalian cells is not yet fully understood in spite of considerable efforts. Much more research is required to elucidate the molecular mechanism of DNA synthesis in cancer cells as well as normal cells. Considering the extensive research activity in the field of mammalian DNA synthesis in Japan and in the U.S., it was thought that this subject would be an appropriate one. In fact, it turned out that both U.S. and Japanese scientists benefitted considerably by having this meeting, with personal information exchange,

initiation of collaborations, exchange of materials, and so on.

The following topics were discussed. Dr. J. Hurwitz reported on the *in vitro* replication of adenovirus DNA. The cell-free extracts which support replicative Ad DNA synthesis have been separated into multiple fractions, which, when combined lead to Ad DNA replication. A full-sized Ad DNA has been synthesized *in vitro*. Ad DNA synthesis was thermosensitive (ts) with nuclear extracts derived from cells infected with ts mutant H5-125 Ad virus which codes for the synthesis of a ts adeno DNA binding protein. Ad DNA synthesis in this system was found to be sensitive to aphidicolin, suggesting involvement of DNA polymerase γ in the replication of adenovirus DNA. He analysed structural forms of Ad DNA synthesized *in vivo*, or in isolated nuclei, in the presence of an inhibitor of DNA polymerase α (aphidicolin) or a γ-polymerase inhibitor (dideoxythymidine triphosphate, ddTTP). The inhibitory effects of aphidicolin and ddTTP are additive suggesting that DNA polymerases α and γ catalyze separate steps in the replication pathway of Ad DNA. An analysis of the viral replicating forms accumulated in the presence of these inhibitors was consistent with the concept that DNA polymerase γ can catalyze strand displacement synthesis. Dr. S. Yoshida reported his recent observation on DNA polymerases α and β. By using inhibitors such as araC, aphidicolin and dideoxythimidine of DNA synthesis *in vivo*, he proposed a model in which DNA polymerase α is involved in replication, while polymerase β participates in repair synthesis. In addition, he was able to separate polymerase α into three distinct molecular species. Dr. A. Matsukage described two template-primer systems to analyse DNA chain elongation mechanisms by highly purified DNA polymerase α, β and γ, using denatured DNA-3'-(dT)n with (rA) $_{12\sim20}$ primers for DNA polymerase α and β, or (rA)n with (dT) $_{12\sim18}$ primers for DNA polymerase β and γ. The results indicated that the chain elongation mechanism of DNA polymerase α, β and γ are quite different from each other. Dr. F. Hanaoka reported the presence of two forms of DNA polymerase α (P_1 and P_2) in HeLa cells which have different affinities for DNA. He proposed that the P_1 enzyme is involved in DNA replication, while P_2 enzyme is involved in DNA repair synthesis. His conclusion was based on:
(1) inhibition of the enzymes with the inhibitors aphidicolin and ddTTP; (2) changes of the activities during the cell cycle; (3) formation of Okazaki pieces with P_1 enzyme; (4) use of mouse mutant cells which decreased the activity of only the P_1 enzyme; (5) use of mouse mutant cells which decreased the activity of only the P_1 enzyme during a temperature shift-up; and (6) lack of the DNA repair reaction after extraction of the P_2 enzyme from cell nuclei. Dr. T. Okazaki reported recent progress on identification of the exact location of initiation sites of DNA replication of the prokaryotic genome. Very elegant method clearly demonstrated that the sequence of the complementary strand, 3' CTG$^{G}_{A}$ 5", is a signal for the primer synthesis in T7 phage. In the case of replication of *E. coli* oriC region, there were two clusters of the transition sites of RNA to DNA. Each cluster of the transition nucleotides consisted of three neighboring nucleotides. Dr. M. Goulian also clearly demonstrated

the presence of a riboorigonucleotide moiety in nascent DNA in mammalian cells. Dr. D. Korn reported isolation and extensive purification of DNA-dependent ATPase from the cytoplasm of human tissue culture cells, and discussed possible involvement of the enzyme during DNA replication in mammalian cells as a ENA unwinding enzyme. Dr. K. Koike presented results on isolation and properties of DNA-dependent ATPase from rat liver mitochondria. Both Drs. L. Grossman and M. Sekiguchi reported their recent results on the enzymology of DNA repair. In addition they discussed the implication of specificity of various endonucleases in determining the various pathways of repair. Dr. Sekiguchi also described the usefulness of plasmolysed cells of *E. coli* for studies on DNA repair mechanism. He was able to detect the umuC gene product, which is necessary for induction and fixation of mutation after UV-irradiation. Dr. M. Saneyoshi reported on the design and synthesis of various novel deoxynucleoside triphosphate analogues which are modified in the 2'- or 3'-position, or both, of the sugar moiety and a selected position of the aglycones of natural substances. It was found that substitution of the hydroxyl group in the 3'-position of the sugar portion caused marked selective inhibition for specific DNA polymerases. In addition, he showed the usefulness of 6-thio-dGTP for isolation of nascent DNA by Hyagarose. Dr. T. Seno reported on mouse FM3A cell mutants which are resistant to aphidicolin. DNA systhesis by these permeabilized cells was found to be 100 times more sensitive to the drug than isolated DNA polymerase α. All the mutants showed a greatly increased dATP pool and an increased sensitivity to bleomycin, suggesting that *in vivo* aphidicolin may have another target besides polymerase α. Drs. T. Kakefuda and H. Maeda reported on the mode of action of benzo(a)pyrene (BP) and neocarzinostatin, respectively with respect to inhibition of DNA synthesis.

In conclusion, participants from both the U.S. and Japan found the meeting extremely useful. There were very stimulating discussions throughout all of the topics presented. Since a similar type of international meeting had not been held for several years, this meeting was extremely informative for all of the participants. It provided an excellent summary of the research on mammalian DNA replication and focused attention on the most important areas for future research. U.S. participants found the new deoxynucleoside triphosphate analogues which Dr. Saneyoshi synthesized very useful for enzymatic study on DNA replication, and agreements for material exchange were made. New personal contacts between U.S. and Japanese participants were made, warm friendships were generated and new collaborations were started during this meeting.

4. PLANS FOR FUTURE MEETINGS
(in the 1980 fiscal year)

1) Seminar on "Biochemical Epidemiology"
   Honolulu, Hawaii, February 10 - 12, 1981
   Organizers: Dr. A. H. Conney, Dr. S. Nishimura
2) Seminar on "Interspecies Correlations in Chemical Carcinogenesis"
   Tokyo, March 19 - 21, 1981
   Organizers: Dr. C. C. Harris, Dr. S. Takayama

5. SEMINAR AGENDA AND PARTICIPANTS

1) Seminar on "Gastrointestinal Tract Cancer"
Honolulu, Hawaii, March 3 - 6, 1980

AGENDA

March 3 9:00 - 9:30

Dr. Sugimura — New Direction of U.S.-Japan Cooperative Research
Introductory Remarks: Dr. Piette
Dr. Weisburger

I. Epidemiology (Dr. Sugimura, Chm.)

9:30 - 9:35	Dr. Sugimura,	Opening Remarks
9:35 - 10:05	Dr. Hirayama	Current status of the epidemiology of stomach and colon cancer with special reference to life style risk factors.
10:05 - 10:35	Dr. Weisburger	Metabolic epidemiology of stomach and colon cancer.
10:35 - 11:00		(Coffee and General Discussion)
11:00 - 11:30	Dr. Copeland	The United States large bowel cancer project Summary report of the current status 1979
11:30 - 12:00	Dr. Tominaga	From descriptive to analytic epidemiology of stomach and colon cancer.
12:30 - 2:00		(Lunch)

II. Pathology, Pathogenesis, Precancerous Lesions
(Dr. Wattenberg, Chm.)

2:00 - 2:05	Dr. Wattenberg,	Opening Remarks
2:05 - 2:35	Dr. Hirota	Histogenesis of human gastric carcinoma: Significance of adenoma and chronic gastritis as precancerous lesions.
2:35 - 3:05	Dr. Stemmermann	Gastric cancer in Hawaii Japanese
3:05 - 4:00		(Coffee and General Discussion)
4:00 - 4:30	Dr. Correa	Pathology of gastric cancer precursor lesions
4:30 - 5:00	Dr. Muto	Comparative pathology of precancerous and cancerous lesions of colon.
5:00 - 5:30	Dr. Furihata	Irreversible change in pepsinogen isozyme found during early stage of gastrocarcinogenesis by MNNG.

March 4

III. Experimental Models (Dr. Hirayama, Chm.)

9:00 - 9:05	Dr. Hirayama,	Opening Remarks
9:05 - 9:35	Dr. Takayama	Degraded careageenan colorectal carcinogenesis in rats.
9:35 - 10:05	Dr. Weisburger	The role of fat and fiber as studied in experimental models for colon cancer.

10:05 - 11:00		(Coffee and General Discussion)
11:00 - 11:30	Dr. Sugimura	Experimental model: Past and future
11:30 - 12:00		General Discussion
12:00 - 2:00		(Lunch)

IV. Genetic Background (Dr. Stemmermann, Chm.)

2:00 - 2:05	Dr. Stemmermann,	Opening Remarks
2:05 - 2:35	Dr. Kitamura	Spontaneous development of forestomach papilloma and prepyloric ulcer in genetically mast cell depleted W/W^v and Sl/Sl^d mice
2:35 - 3:05	Dr. Murata	Genetics as a determinant in colon cancer
3:05 - 4:00		(Coffee and General Discussion)
4:00 - 4:30	Dr. McKeen	Genetic diseases as an aid to pathogenesis studies
4:30 - 5:00	Dr. Lipkin	Familial polyposis: New data
5:00 - 5:30		General Discussion

March 5

V. High Risk Human Population (Dr. Takayama, Chm.)

9:00 - 9:05	Dr. Takayama,	Opening Remarks
9:05 - 9:35	Dr. Lipkin	Memorial Hospital registry of population groups at high risk for cancer of the large intestine
9:35 - 10:05	Dr. Matsukura	Intestinal metaplasia and its implications in human gastric cancer
10:05 - 11:00		(Coffee and General Discussion)

VI. Possible Carcinogens, Promoters, and Inhibitors (Dr. Correa, Chm.)
(Brief remarks and discussion)

11:00 - 11:05	Dr. Correa,	Opening Remarks

A. Discussion on agents for colon cancer

11:05 - 12:00	Dr. Bruce	Mutagens and nitrosamines in human feces
	Dr. Wilkins	Organization and *in vitro* production of a human fecal mutagen
	Dr. Mower	Fecal mutagens in Japanese living at high risk and at low risk
	Dr. Takayama	Possible carcinogen in pyrolysis product
12:00 - 2:00		(Lunch)
2:00 - 3:15	Dr. Weisburger	Mutagens and possible carcinogens in fried foods
	Dr. Nigro	The variable nature of the etiological factors in cancer of the intestinal tract
	Dr. Furihata	Our recent findings of mutagens in promoters in relation to experimental colon carcinogenesis.
	Dr. Wattenberg	Inhibitors of large bowel carcinogenesis
3:15 - 4:00		(Coffee and General Discussion)

B. Discussion on agents for gastric cancer

4:00 - 5:15	Dr. Kamiyama	Gastric cancer mortality and dietary

		mutagenicity
	Dr. Tannenbaum	Gastric cancer
	Dr. Mirvish	Formation of methylnitrosourea in the rat stomach, and nitrosation-denitrosation of foodstuffs to produce alkylureas
	Dr. Weisburger	Nitrosation of fish: A source of gastric carcinogens
	Dr. Takahashi	Enhancing effects of sodium chloride on gastric carcinogenesis
	Dr. Sugimura	Do environmental chemicals exist in 3 dimensional spaces with axes of mutagenic, promotive and carcinogenic potentials: Possible new naturally occurring promoters
5:15 - 5:30		(General Discussion)

March 6

VII. Intervention Study (Dr. Copeland, Chm.)

9:00 - 9:05	Dr. Copeland,	Opening Remarks
9:05 - 9:35	Dr. Bruce	An intervention study of the effect of ascorbate and alpha-tocopherol on recurrent polyps
9:35 - 10:05	Dr. Narisawa	Animal model of chemotherapy and chemoprevention of colonic tumors
10:05 - 10:30		(Coffee and General Discussion)
10:30 - 11:00	Dr. Correa	Report on a double-blind, randomized intervention trial of gastric cancer precursor lesions
11:00 - 11:30	Dr. Oshima	Evaluation of intervention trials in stomach cancer
11:30 - 12:00		(General Discussion)

Closing Remarks: Dr. Bruce
Dr. Hirayama

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2) Seminar on "Molecular Mechanism of DNA Synthesis in Cancer Cells"
International House, Tokyo, Japan, March 6 - 8, 1980

AGENDA

Thursday, March 6

11:00 - 12:00	Registration
	(Lunch)
	Official Opening
1:30 - 2:00	Dr. Susumu Nishimura
	Dr. Katsuro Koike
	Mechanism of Initiation of DNA Synthesis
	Chairperson: Dr. D. Korn
2:00 - 2:40	Dr. Jerard Hurwitz
	Studies on the *In Vitro* Replication of Adenoviral DNA
2:40 - 2:50	Discussion
2:50 - 3:20	(Coffee Break)
3:20 - 3:50	Dr. Tsuneko Okazaki
	Mapping of Initiation Sites of DNA Replication on Prokaryotic Genomes
3:50 - 4:00	Discussion
4:00 - 4:30	Dr. Katsuro Koike
	Replication of Mitochondrial DNA: Nucleotide Sequence of the Origin and DNA-dependent ATPase
4:30 - 4:40	Discussion

Friday, March 7

	DNA Polymerases and Their Reaction Mechanisms
	Chairpersons: Dr. J. Hurwitz
	Dr. K. Koike
10:00 - 10:40	Dr. David Korn
	Mechanisms of Catalysis of Human DNA Polymerases α and β
10:40 - 10:50	Discussion
10:50 - 11:20	(Coffee Break)
11:20 - 11:50	Dr. Shonen Yoshida
	DNA Polymerase α from Calf Thymus: Catalytic Properties and a Possible Cooperation with Terminal Deoxynucleotidyl Transferase
11:50 - 12:00	Discussion
	(Lunch)
1:30 - 2:10	Dr. Arthur Weissbach
	A Possible Role for DNA Polymerase γ
2:10 - 2:20	Discussion
2:20 - 2:50	Dr. Akio Matsukage
	Difference in DNA Chain Elongation Mechanism of DNA Polymerases α, β and γ
2:50 - 3:00	Discussion
3:00 - 3:30	(Coffee Break)
3:30 - 4:00	Dr. Mineo Saneyoshi
	The Design, Synthesis and Inhibitory Effects of 2'-Deoxyribonucleosides 5'-triphosphate analogues on Eukaryotic DNA-dependent DNA Polymerases

4:00 - 4:10	Discussion
6:00 - 8:00	Reception

Saturday, March 8

DNA Repair and Enzymes

Chairpersons: Dr. A. Weissbach
Dr. M. Sekiguchi

10:00 - 10:40	Dr. Lawrence Grossman Enzymology of DNA Repair
10:40 - 10:50	Discussion
10:50 - 11:20	(Coffee Break)
11:20 - 11:50	Dr. Mutsuo Sekiguchi Mechanism of DNA Repair as Revealed by Artificial Introduction of Enzymes into Viable Cells
11:50 - 12:00	Discussion
	(Lunch)
1:30 - 2:10	Dr. Mehren Goulian Presence of Uracil in DNA of Cells Treated with Inhibitors of Thymidylate Synthetase
2:10 - 2:20	Discussion
2:20 - 2:50	Dr. Takeshi Seno Mouse FM3A Cell Mutants Resistant to Aphidicolin, an Inhibitor of DNA Polymerase α
2:50 - 3:00	Discussion
3:00 - 3:30	(Coffee Break)
3:30 - 4:10	Dr. Tsuyoshi Kakefuda The Structural and Functional Modification of DNA by Benzo(a)pyrene diol-epoxide I
4:10 - 4:20	Discussion
4:20 - 4:50	Dr. Fumio Hanaoka Involvement of DNA Polymerase α in DNA Replication and Repair in HeLa Cells
4:50 - 5:00	Discussion
5:00 - 5:30	Dr. Hiroshi Maeda Subcellular Action of Neocarzinostatin: Intracellular Incorporation, DNA Breakdown and Cytotoxicity
5:30 - 5:40	Discussion
5:40 - 6:00	Closing Remarks Dr. David Korn

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6. SUMMARY REPORTS OF EXCHANGE SCIENTISTS

1) MASAKAZU HATANAKA, M.D., PH.D., National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205

Host Institution: Professor Tsutomu Sugahara, Faculty of Medicine, Kyoto University, Kyoto, Japan

Dates of Visit: September 10 to October 20, 1979

Summary of Activities:

Indian muntjac (Muntjacus muntjak) cells have a diploid chromosome number 6 in the female and 7 in the male, the lowest number yet described in a mammal, and have maintained diploidy after many passages in culture. We have successfully transformed the cells by a xenotropic murine sarcoma virus, 43-2 XV, and isolated morphologically transformed permanent lines that retain a stable diploid chromosome number (M. Hatanaka and R. Klein, "Tumorigenicity of Indian Muntjac Diploid Cells by the Proviral Integration of Sarcoma Gene of a Mouse Retrovirus" *Journal of Experimental Medicine*, 150: 1195-1201, 1979). These diploid clones of Indian muntjac permanent cells have physical, numerical and cytogenetic advantages to study and score systematically chromosomal aberrations (CA) and sister chromatid exchanges (SCE) induced by environmental mutagens and carcinogens.

Professor Sugahara in the Department of Experimental Radiology, Faculty of Medicine, Kyoto University, Kyoto, Japan has been interested in using our permanent lines of Indian muntjac for studies of carcinogenesis and mutagenesis. Thus, I worked with the staff of Dr. Sugahara using his facilities during my stay in Japan under the auspices of the U.S.-Japan Cooperative Cancer Research Program from September 10 to October 21, 1979.

Six alkylating agents, four N-nitroso- and two methane-sulfonate compounds were tested for the induction of chromosomal aberrations (CA) and sister chromatid exchanges on one of our clonal isolates, 12-1-58. The magnitudes of detecting sensitivity of CA and SCE on the Indian muntjac chromosomes after mutagenic exposures were found to be similar, implying the greater advantages by use of Indian muntjac cells for the screening of mutagens and carcinogens compared to other mammalian cells as an indicator. Scoring CA in the large and easily identifiable 6 chromosomes of Indian muntjac requires a minimal degree of skillfulness. These features may be exploitable in the standardization of CA screening and useful to regulatory institutions and hospitals. With certain carcinogens that fail to induce SCE, such as X-ray, we were able to rapidly and quantitatively detect CA of Indian muntjac chromosomes. These effects were much easier to detect than in other mammalian chromosomes.

Some of the results will be published in the *Journal of Mutation Research* by Peter Raff and Tsutomu Sugahara entitled "Sister Chromatid

Exchanges, Chromosomal Aberrations and Cytotoxicity in Cultured Indian muntjac cells treated with Alkylating Agents." We have also investigated chromosome changes in 60 clonal isolates of Indian muntjac, collaboration with Dr. Masao Sasaki. In preliminary studies we found two unusual translocations in two clonal isolates of Indian muntjac; (X/X,3/3) in 12-1-60 T clone and (1p/X, 1q/3) in 12-(1)-01 clones. Both clones produce highly malignant tumors in nude mice (M. Hatanaka and R. Klein, *Journal of Experimental Medicine*, 150, 1195-1201, 1979). These unique translocations have never been found in the parental cells.

The results reported here have been obtained under the auspices of the U.S.-Japan Cooperative Cancer Program during my stay in Japan. These informations may provide a useful basis for establishing a new sensitive method for CA screening of mutagens and carcinogens, and new insights for studies on chromosomal organization and chromosomal rearrangements.

2) NEIL ELLIOT SPINGARN, American Health Foundation, Valhalla, New York 10595

Host Institution: Dr. Takashi Sugimura, National Cancer Center Research Institute, Tokyo, Japan

Dates of Visit: October 3, 1979 - December 13, 1979

Summary of Activities:

The purpose of my visit to Japan was to collaborate with Drs. Sugimura and Matsushima on isolation and identification of the principal mutagens from cooked beef. This is part of an ongoing project investigating the health effects of food cooking procedures and their postulated role in the etiology of human cancer, particularly colonic cancer. We succeeded in purifying and partially identifying one of the two mutagens present, and partially purified the second mutagen. A paper describing this work is currently in press. [Spingarn, N.E. et al, *Cancer Letters*, 9, 177-183 (1980). "Formation of Mutagens in Cooked Foods. III: Isolation of a Potent Mutagen from Beef."]

This project was successful in achieving its objectives since by combining our individual techniques, both laboratories (ours and theirs) can now purify mutagens from food more effectively. A major step forward has resulted from isolation of this mutagen from beef. We plan to continue our very fruitful collaboration in the pursuit of mutagens/carcinogens in food. Visits to or from Japan may be desirable at a later date to continue this collaboration.

3) LYNNE A. HAROUN, B.A., M.P.H., Department of Biochemistry University of California, Berkeley, California

Host Institution: Dr. Takashi Sugimura, Director, National Cancer Center Research Institute, Tokyo, Japan

Dates of Visit: November 1, 1979 to January 31, 1980

Summary of Activities:

a) The Testing of Polychlorinated Hydrocarbons in the *Salmonella* Assay: Activation by House Fly S9

Almost every member of the class of multiply chlorinated compounds that has been tested in experimental animals has been shown to be a carcinogen. This important class of industrial and agricultural compounds includes such widely used chemicals as the solvents, carbon tetrachloride and chloroform; and the pesticides, aldrin and DDT. However, most of these compounds are not detected as mutagens in the *Salmonella*/Ames test. Since most carcinogens are mutagens in the assay, we have been concerned with developing modifications of the *Salmonella* assay for the detection of these compounds. There are several possible explanations for the negative response in the *Salmonella* assay. These compounds have relatively low chemical and metabolic reactivity and the S9 mix (prepared from rat liver) routinely used in the assay may not metabolize these compounds to active intermediates, either because essential cofactors are missing, or the enzymes needed for activation are not present at sufficiently high levels. Another possibility is that many of these compounds are metabolized to free radicals whose half-lives are so short that they are reacting with other components of the reaction mixture before reaching the target DNA. Other mechanisms under consideration are that these compounds act indirectly through a common mechanism, possibly through the peroxidation of lipids and generation of free radicals or malonaldehyde.

My work in Japan was concerned with one aspect of this problem the use of S9 that would be able to better activate this class of compounds. The work involved the preparation and testing of an S9 fraction from domestic house flies. Insect microsomal fractions are able to catalyze several different reaction types, being similar in metabolic versatility to mammalian liver microsomes. Strains of house flies were obtained from Dr. T. Hiroyoshi at Osaka University that were resistant to some of the chlorinated pesticides. While the biochemical basis for resistance is not known it was thought that an S9 prepared from both resistant and wild-type strains would be a useful tool for looking at the metabolism of these compounds. The *Salmonella* test was used to monitor the generation of reactive mutagenic metabolites.

An S9 fraction from both wild-type and resistant strains of house fly larva was prepared and then used to screen a number of known mutagens in the *Salmonella* assay. It was necessary to first develop techniques for preparing a sterile fraction. Five compounds, benzo(a)pyrene, 7,12-dimethylbenzanthracene, acetylaminofluorene, tris(2,3-dibromopropyl)phosphate and sterigmatocystin were then screened in the assay. Four of the five compounds were activated by the fly larva S9. In these preliminary experiments it was shown that: (1) The larva S9 was able to metabolize known mutagens to their active metabolites; (2) There were differences in the metabolic activity of the S9 from wild-type and resistant strains and that these differences

were compound dependent; and (3) The activity of larva S9 ranged from less active to more active than rat liver S9, depending on the compound being tested. Eleven chlorinated hydrocarbons[1] representing a variety of structural types were screened in the *Salmonella* assay using the house fly S9. All eleven compounds were negative in the assay.

Further experiments with fly S9 fractions included: (1) The preparation of S9 fractions from PCB, DDT or aldrin induced fly larvae, and (2) The preparation of S9 fractions from induced and uninduced adult flies (reports in the literature suggest that enzyme levels in adult flies are higher than in larvae). However, negative results were obtained when the chlorinated hydrocarbons were tested with these S9 fractions.

Although the house fly S9 was not able to metabolize the polychlorinated hydrocarbons to intermediates mutagenic to *Salmonella* it was possible that some of the other compounds that are false negatives (carcinogens/nonmutagens) in *Salmonella* would be activated by the house fly S9. There are a few compounds that are negative in *Salmonella* when tested in the presence of rat liver S9, but positive when tested in the presence of an S9 fraction from a different species. I screened several compounds from different chemical classes in the *Salmonella* assay with the fly S9. However, these compounds were also negative in the assay.

In conclusion, the house fly S9 was shown to be capable of metabolizing several indirect acting mutagens to their active mutagenic intermediates. However, the polychlorinated hydrocarbons and other compounds tested (i.e., other false negatives) were not activated by the house fly S9.

b) The Mutagenicity of Edible Seaweeds

During the last three years it has been shown that mutagens are present in many of the foods we eat. These include naturally occurring compounds such as quercetin and quercetin-glycosides that are present in many fruits and vegetables, and the very potent mutagens found in broiled meat and fish that are formed during the broiling process. Intensive work is currently being carried out at a number of different laboratories to identify those mutagens in foods that might be significant factors in causing human cancers. A useful approach to the study of dietary causes of cancer is to look at the mutagenic activity of foods that are unique to different population groups.

Seaweeds, an important constituent in the Japanese diet, meet this requirement. They also contain a number of brominated and chlorinated hydrocarbons, a class of compounds that often have high mutagenic and carcinogenic activity. While in Japan, I tested for mutagenicity five different edible seaweeds that are popular in Japanese cooking. Methanol and chloroform: methanol extracts of

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[1]Compounds tested were dieldrin, aldrin, p,p'DDD, o,p' and p,p'-DDT, p,p'-DDE, CCl_4, $CHCl_3$ and α and γ BHC.

each seaweed were prepared and then tested in the *Salmonella* mutagenicity test. All five seaweeds were weakly mutagenic in the assay. Four of the five seaweeds were most active on the *Salmonella* tester strain TA98, in the presence of S9. While there was not time to identify the active principle in the seaweeds, these results would be consistent with the hypothesis that the mutagenicity was due to the presence of quercetin in the seaweeds. One seaweed was most active on strain TA100 in the absence of S9. Preliminary experiments attempting to concentrate the mutagenic compound(s) resulted in the complete loss of activity.

Based on these preliminary results, studies on the mutagenicity of edible seaweeds may be continued in Dr. Sugimura's laboratory in Japan, or by Dr. Ames in collaboration with Dr. Lowell Hager at the University of Illinois.

4) ARTHUR WEISSBACH, PH.D., Department of Cell Biology, Roche Institute of Molecular Biology, Nutley, New Jersey 07110

Host Institution: Dr. Katsuro Koike, Cancer Institute (Japanese Foundation for Cancer Research)
Sponsored the meeting entitled "Molecular Mechanism of DNA Synthesis in Cancer Cells" which was held at the International House of Japan, Tokyo
Dr. Kiyoshi Kurahashi, Osaka University
Dr. Osamu Hayaishi, Kyoto University
Dr. Taijo Takahashi, Aichi Cancer Center

Dates of Visit: February 27, 1980 through March 10, 1980

Summary of Activities:

In conjunction with my participation in the meeting on molecular mechanism of DNA synthesis in cancer cells in Tokyo, I spent additional time in Japan (from February 27 - March 10, 1980) visiting and consulting at the Osaka University, Kyoto University and the Aichi Cancer Center. I also presented seminars on my work on mammalian DNA polymerase at these institutions.

The exchange of information with Japanese scientists was valuable in planning future research. It provided information which will enable me to avoid non-productive work and suggested new possibilities to us. The meeting "Molecular Mechanism of DNA Synthesis in Cancer Cells," held in Tokyo, provided a valuable forum for the exchange of knowledge between the United States and Japanese scientists. Most of the information exchanged had not been previously published and was, therefore, new. Several possible collaborative research projects between my laboratory and some Japanese laboratories were discussed and will, hopefully, be initiated in the near future.

5) DAVID KORN, M.D., Department of Pathology, Stanford University School of Medicine, Stanford, California

Host Institution: Dr. Katsuro Koike
Cancer Institute, Tokyo

Dates of Visit: March 6-8, 1980

Summary of Activities:

I wished to let you know that the US-Japan Conference was extremely successful in all respects and I gathered from my subsequent conversations with Drs. Sugano and Sugimura that there is some considerable interest on the Japanese side in trying to continue this series of meetings, on an alternating basis, perhaps every two years. I personally believe such a schedule of meetings would be profitable and justifiable, but obviously, I do not know precisely how such decisions are made under the aegis of the US-Japan Cooperative Program.

In addition to the meeting itself, I very much enjoyed my visits to Kyoto University, Aichi Cancer Center, the Cancer Institute, the National Cancer Center and Saitama Cancer Center, and in the latter four institutions, I delivered lectures that ran between 90 and 120 minutes to a well-informed and gratifyingly interactive audience. I also enjoyed my consultations with workers in each institution who are engaged in relevant research activities pertaining to the regulation of DNA replication and repair in a variety of mammalian cell systems.

The physical facilities in the several cancer institutes were quite impressive, as was the general quality of the science being performed, particularly by the younger generation of investigators.

6) TAKESHI HIRAYAMA, M.D., Chief, Epidemiology Division, National Cancer Center Research Institute

I visited the U.S. from August 5 - August 25, 1979 under the Scientist Exchange Program of the U.S.-Japan Cooperative Cancer Research Program.

Most of the work was done in the Clinical Epidemiology Branch National Cancer Institute. Precious assistance and cooperation was given by Dr. Robert Miller, the Chief of the Branch.

The main subject studied was the Comparative Epidemiology of Chemical carcinogenesis and Radiation carcinogenesis.

REC (rem-equivalent-chemical) is a recently developed term describing the concentration of a chemical mutagen that produces an amount of genetic damage equal to that produced by 1 rem of chronic irradiation. This notion was developed from *in vitro* and/or *in vivo* experiment. A need was felt to develop a similar concept in humans. For that purpose, a dose-response relationship between life time dose of cigarette smoking and cancer mortality was compared with similar dose-response relationships between the exposure dose of radiation and cancer mortality. The materials used were: (1) Ongoing

prospective study for 265,115 adults aged 40 and above in Japan (Hirayama, 1966-78) and (2) Ongoing prospective study for 109,000 A-bomb survivors and controls in Hiroshima and Nagasaki, 1950-74. A detailed comparison revealed that the smoking of one cigarette is equivalent to 1-4 millirad in terms of cancer causing effect. A similar comparison was made for cancers of specific sites, (e.g., lung cancer).

On August 13, these findings were reported and discussed in a seminar jointly held by the Environmental Epidemiology Branch and the Clinical Epidemiology Branch, NCI.

On August 15 and 16, a workshop was held on Mutagen Load, with Dr. Hollaender as the Chairman. Both Dr. Sugimura and I attended from Japan. In this workshop again, the above results were discussed. Points raised were as follows:

1. In the case of A-bomb survivors, exposure was only once. In the case of cigarette smoking, it is a continued/repeated exposure. Such differences must be kept in mind.
2. A more suitable mathematical model should be sought in addition to a linear model.
3. Similar studies should be attempted with other chemical carcinogens.

In relation to these points, the lung cancer mortality for smokers and non-smokers in radium miners was studied based on official reports and available literature. For lung cancer, one cigarette was noted to be equivalent to 7.5-15 millirad.

On August 20 - 24, the Gordon Conference on Cancer Etiology in Humans was attended by both Dr. Sugimura and myself, and several new clues for future epidemiological research on cancer were obtained.

7) KAZUO UMEZAWA, Institute of Medical Science, University of Tokyo

I visited the United States between August 18, 1979 and October 19, 1979 to study the mechanism of tumor promotion cooperatively with Dr. I. B. Weinstein, College of Physicians and Surgeons of Columbia University.

Prior to joining Dr. Weinstein's research group, I attended the Gordon Cancer Conference in New London, New Hampshire, together with Dr. T. Sugimura, where the mechanism of carcinogenesis at the cellular level was mainly discussed. I went to New York on August 25 and began to work on the cellular action of tumor promoters and membrane active compounds. During my relatively short stay at Columbia University, I completed two research projects as follow:

a) Inhibition of Cellular Binding of Epidermal Growth Factor (EGF) by Staphylococcal Delta-Hemolysin

Recent studies indicate that the potent tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) at nanomolar concentrations specifically inhibits the binding of epidermal growth factor (EGF) to its cell surface receptor. Staphylococcal delta-hemolysin, a polypeptide having the molecular weight of about 3500 also inhibited

cellular EGF binding. The addition of 2.5 µg/ml of delta-hemolysin resulted in a rapid and marked inhibition of EGF binding in rat embryo cells. The dose required to produce 50% inhibition was about 2 µg/ml and complete inhibition was obtained with about 5 µg/ml. Parallel studies indicated that no cytolytic effect was observed at concentrations as high as 10 µg/ml of delta-hemolysin, after incubation for 2 hours at 37°C, although higher concentrations were toxic.

Delta-hemolysin also inhibited EGF binding in HeLa cells. With these cells 50% inhibition was observed at about 10 µg/ml and again no cytolytic effect was observed at this concentration of delta-hemolysin. HeLa cells displayed slight swelling at 50 µg/ml of delta-hemolysin after 1 hour incubation. Inhibition of EGF binding by delta-hemolysin was not affected by 50 µg/ml of hydrocortisone or dexamethasone of 25 µg/ml of mepacrine, agents reported to inhibit membrane phospholipases.

Studies on the release of arachidonic acid were done with the 10T½ mouse embryo cells to compare the effects with that previously reported for TPA. At 1 µg/ml delta-hemolysin proved to be a potent inducer of the release or arachidonic acid metabolites from the ^{3}H-arachidonic acid prelabelled cells. Chromatographic analysis of the media showed that free arachidonic acid and significant amounts of prostaglandins E2 and F2 α were released in cells exposed to 1 µg/ml of delta-hemolysin.

These data do not, of course, indicate that the primary site of binding of these compounds is the same. Both TPA and delta-hemolysin stimulate lymphocyte mitosis and both induce epidermal inflamation. It will be of interest to determine to what extent delta-hemolysin shares other effects with tumor promoters.

b) Inhibition of Cellular Binding of Epidermal Growth Factor (EGF) by Phorbol Esters in Various Types of Cell Cultures

Inhibition of EGF binding by phorbol esters was studied with hamster, rat, and mouse embryo cells. TPA and phorbol-12,13-didecanoate inhibited EGF binding in 3 cell cultures at 0.05-0.1 µg/ml. Phorbol-12, 13-diacetateand phorbol did not inhibit EGF binding even at 10 µg/ml. 4-O-Methyl-TPA, a weak tumor promotor, inhibited EGF binding at 0.2 µg/ml in 3 primary cell lines. Therefore, the receptors for phorbol esters appear to be similar in the 3 rodent cell cultures; they may differ, however, from the receptors in HeLa cells where 4-O-methyl-TPA did not inhibit EGF binding.

Collaborative studies between I. B. Weinstein, T. Sugimura and myself on membrane effects of the compound teleocidin were also begun during this visit and are yielding interesting similarities with the effects of TPA.

8) NORIO MATSUKURA, National Cancer Center Research Institute

Host Institution: (1) National Cancer Institute,
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(2) Kuakini Medical Center, Honolulu,
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Dates of Visit: from September 1, 1979 to September 24, 1979

Summary of Activities:

I took specimens of experimental gastric cancer and intestinal metaplasia in animals which were produced at the National Cancer Center Research Institute, Tokyo, to the United States to be examined jointly by Dr. Harold L. Stewart, Scientist Emeritus of the National Cancer Institute (NCI) and myself through the U.S.-Japan Cooperative Cancer Research Program. The following points have been agreed between Dr. Stewart and me.

1. The sequential morphological changes of the glandular stomach of rats induced by a weak carcinogen, N-propyl-N'-nitro-N-nitrosoguanidine (PNNG) were different from that of a strong carcinogen, N-methyl-N'-nitrosoguanidine (MNNG), since in early stages, erosion or ulcer were not observed and intestinal metaplasia was observed before induction of gastric carcinoma. These processes of carcinogenesis by PNNG resemble those in the human more than those produced by MNNG. Therefore, the experimental gastric carcinoma produced by PNNG in rats seems to be a better experimental model for human gastric cancer.
2. According to Dr. Harold L. Stewart, the histopathology of the minute cancer in dogs induced by N-ethyl-N'nitro-N-nitrosoguanidine (ENNG) is very similar to that of the initial stage of small intestinal cancer in mice, which was induced by Dr. Harold L. Stewart in NCI. By examination of the set of slides on experimental cancer of the small intestine in mice at NCI, I confirmed the similarity in origin between the intestinal type of gastric cancer in dogs and cancer of the small intestine in mice.

The above points were confirmed by Dr. Harold L. Stewart under the microscope and the results obtained will be submitted for publication, as studies supported by the U.S.-Japan Cooperative Cancer Research Program.

An additional accomplishment of this visit was to obtain information about registry for animal tumors. In the Tumor Registry of the NCI, records of autopsy on experimental animals are computerized and all of the slides are readily available. The work of this tumor registry is important from the point of view of education of researchers and the exchange of information in this field. Japan has not yet set up this type of system for registering experimental animal tumors. I was strongly impressed with the necessity of establishing this system in Japan in the near future. Therefore, booklets and forms on the tumor registry were brought back by myself.

Recent experimental results on intestinal metaplasia were discussed with Dr. Grant N. Stemmerman, Director of Laboratories of Kuakini Medical Center. Data were exchanged related to intestinal metaplasia of rats induced by chemical mutagens-carcinogens. Dr. Stemmerman reciprocated with data which showed that mutagenicity could be detected in the mucosa of the regions of the intestinal metaplasia in resected specimens of human stomach. These data suggest

that intestinalization of the human stomach might be induced by carcinogen in foods. There was good agreement on the necessity for cooperative studies on intestinal metaplasia.

9) HIROYUKI SHIMIZU, Epidemiology Division of Aichi Cancer Center Research Institute

a) Epidemiological Study of Environmental Factors in Lung Cancer

Since October, 1979 I have been conducting a descriptive epidemiological study on lung cancer in Los Angeles at the Department of Community Medicine, School of Medicine, University of Southern California (Chairman: Professor Brian E. Henderson, M.D.). I have finished data collection and analysis, and I am presently writing up a manuscript for publication.

b) Epidemiological Study on Metabolic and Endocrinological Characteristics of Prostate Cancer

Following a suggestion by Dr. Henderson, I have been planning to conduct a case-control study on prostatic cancer in Los Angeles. I have completed a questionnaire and am ready to mail it to study subjects. For the present, I plan to collect the questionnaires by the end of September, 1980.

10) KAZUKIYO ONODERA, Institute for Virus Research, Kyoto University

Tunicamycin (TM) is the antiviral agent, the structure of which has just been elucidated. It specifically inhibits the formation of N-acetylglucosaminyl pyrphosphorylisoprenol, the first oligosaccharide-lipid intermediate in the lipid-linked pathway of the biosyntheses of asparagine linked glycoprotein. The site which TM attacks appears to be very specific and many investigators have employed TM to determine the role of carbohydrate moieties in various kind of glycoproteins.

Thus, we searched for mammalian cells which were resistant to the action of TM hoping that we might be able to isolate a new type of cell membrane mutant.

Stable clones selected for resistance to TM have been isolated from Chinese Hamster Ovary (CHO) cells. The RM^R phenotype is stable for more than nine months in the absence of the drug. The morphology of TM^R mutants varies from epitheloid to abnormally elongate. The mutants do not display cross-resistant for Con A but are slightly cross-resistant to PHA. Biochemically labeled membrane proteins and glycoproteins of Vesicular stomatitis virus (VSV) grown in the RM^R mutants revealed that the incorporation of radioactive glucosamine was markedly reduced in the mutants. The results indicate that TM^R cells are a novel type of membrane mutant. (J.Cell. Physiol., 101, 149-156, 1979).

We have learned that Dr. L. Baker and Dr. P. W. Robbins have obtained a TM resistant mutants of CHO cells which have a different

genetic background from ours. Therefore, I decided to visit their laboratory and compare these properties and exchange information.

The following points were clarified during my stay at M.I.T.:

1. Formation of Dol-P-P-GlcNAc in the mutants.
   $Dol\text{-}P + UDP\text{-}GlcNAc \longrightarrow Dol\text{-}P\text{-}P\text{-}GlcNAc + UMP$ ---- (1)
   $Dol\text{-}P\text{-}P\text{-}GlcNAc + UDP\text{-}GlcNAc \longrightarrow Dol\text{-}P\text{-}P\text{-}(GlcNAc)_2 + UDP$ ---- (2)
   The enzyme involved in step (1) is a target enzyme of TM. The enzyme in the mutant shows extremely low activity compared with the wild type of cells. The enzyme of step (1) was not TM resistant in our mutants, however, in the TM^R resistant mutant obtained at M.I.T., the enzyme was slightly resistant.
2. Formation of an abnormal compound as lipid oligosaccharide intermediate. One of the mutants have been shown to produce an abnormal intermediate in the reaction shown above. The chemical structure is under investigation at the present time. We think this compound is $Dol\text{-}P\text{-}P\text{-}(GlcNAc)_n$. (n=3 or 4)
3. Genetic crosses between our mutant and a mutant at M.I.T. have been made and are being studied. One of the TM^R mutants showed co-dominancy in the cross.

Future studies with TM^R mutants in cancer research:

1. Clearly TM^R cells are membrane mutants involved in the formation of a common precursor of an oligosaccharide-lipid intermediate. Therefore, we can alter the surface structure of cancer cells dramatically by introducing TM^R mutations.
2. The dominancy of TM^R has stimulated us to clone the TM^R gene into a plasmid. Thus, we are able to use the TM^R character in the genetic manipulations of mammalian cells.

11) YOSHIYUKI KUCHINO, Biology Division, National Cancer Center Research Institute, Tokyo

I visited Dr. Ernest Borek, University of Colorado Medical Center, Denver, for studies on the function of tumor specific tRNA. I also visited Dr. Dezider Grunberger, Institute of Cancer Research, Columbia University, New York, during my stay in the U.S.

During my stay in Denver, from March 4 - 29, 1980, I isolated a large quantity of tumor specific $tRNA^{Phe}$ from Novikoff hepatoma cells, which were collected by Borek's group in advance. This purified $tRNA^{Phe}$ was used later to analyse whether the primary structure of the tumor specific $tRNA^{Phe}$ is different from the normal $tRNA^{Phe}$ and whether the presence of hypomodified Y base is a common feature in all tumor specific $tRNA^{Phe}$. I learned the procedure to prepare cell-free protein synthesizing system from Ehrlich ascites cells, which is dependent on tRNA added in the system. The system was utilized to elucidate the function of tumor-specific tRNA in protein synthesis after I returned to Tokyo. I also discussed the problem of structural characterization of the unknown modified nucleoside which is specifically excreted in the urine of particular cancer patients which has been recognized by Dr. Borek. At Columbia University, I demonstrated a procedure to

purify tRNA by two-dimensional polyacrylamide gel electrophoresis, and obtained pure $tRNA^{Phe}$ species from neuroblastoma cells. I found that: (1) neuroblastoma cells contain at least two different species of tumor specific $tRNA^{Phe}$; (2) Both $tRNA^{Phe}$s contain hypo-modified Y base; and (3) one $tRNA^{Phe}$s has an additional modification in the TΨC-stem. I also discussed the problem of sequencing of tRNA, using a post-labeling technique, with Dr. Grunberger. My visit to the U.S. turned out to be very productive since the work led to the conclusion that alteration of $tRNA^{Phe}$ in tumor cells is due to the aberrant modification of the Y base, but not due to altered different transcription of $tRNA^{Phe}$.

During my visit, I presented two seminars; one, at the University of Colorado, and one at Columbia University.

BEST DOCUMENT AVAILABLE

II. BIOLOGY AND DIAGNOSIS AREA

II. BIOLOGY AND DIAGNOSIS AREA

Program Coordinators: Dr. William D. Terry, U.S.A.
Dr. Yuichi Yamamura, Japan

Principal Advisors:
U.S.A.: Dr. Ira Pastan
Dr. Richard Hodes
Dr. Myron Melamed
Japan: Dr. Yoji Ikawa
Dr. Toshiyuki Hamaoka
Dr. Yoshio Tenjin

1. ADMINISTRATIVE REPORT

A. Seminars

1) Cellular & Molecular Biology Area

Title: *Src* and *Leuk* Genes (Also see p. 39)
Dates: November 12-14, 1979
Place: National Institutes of Health, Bethesda, MD, USA
Number of Participants:
14 - U.S.
8 - Japanese
Summary:

The meeting lasted for 2-1/2 days with a dinner at the end of the first day. There was an equal division of time between formal presentations and informal discussions. A lot of new information was presented and there was an opportunity to discuss in detail some previous work in which there was some disagreement among the investigators present.

The initial talk was by Dr. Karen Beemon who presented evidence that there was specific phosphorylation of tyrosines in Rous sarcoma virus transformed cells. This phosphorylation appears to be catalyzed by the transforming gene product of Rous sarcoma virus. Phosphotyrosines in proteins are novel and of probably great regulatory significance. Next, Dr. Jim Neil discussed recovery of sarcoma proteins from recovered avian sarcoma viruses. Following his presentation, Dr. Hanafusa also discussed similar experiments. It is clear that Rous sarcoma virus can recombine with host sequences to generate new kinds of transforming viruses. This exciting finding is consistent with the notion that a protein very similar to the sarcoma protein is present in normal chicken cells. Dr. Tadashi Yamamoto discussed recent experiments he has carried out on unusual cDNA clones isolated from avian sarcoma virus transformed cells. Dr. Yamamoto presented evidence that there are additional sequences present at the end of certain messenger RNAs present in ASV transformed cells that were previously unexpected. One of the clones he has isolated appears to have a promoter which probably is the site of initiation of Rous sarcoma virus transcription. Dr. Yamamoto also proposed a new model

by which sarcoma-defective varients are generated. Dr. Sadaaki Kawai then discussed a new mutant of Rous sarcoma virus defective in transformation derived from a classical mutant ts-NY68. The afternoon session began with an exciting presentation by Dr. Ray Erikson describing the phosphorylation catalyzed by the Rous sarcoma virus transforming gene product that he has identified. Then Dr. Gilbert Jay described experiments in which phosphorylation of proteins was observed in cell free extract of RSV transformed cells.

Dr. Asim Dasgupta from Dr. Baltimore's laboratory described the characterization of a phosphoprotein from cells transformed by the Abelson strain of murine leukemia virus. This phosphoprotein also contains a phosphotyrosine.

Dr. Oda reviewed work previously done in his laboratory on the phosphorylation of proteins in virally transformed cells. Dr. Yoshikura then described experiments in which there is co-carcinogenesis produce by both viral transformation and chemical transformation.

The morning of the second day was devoted initially to studies by Drs. Shih and Scolnick on the characterization of the transforming protein of Harvey sarcoma virus. This protein is a membrane protein and has the capacity to bind GTP. Dr. Tsuchida also described studies on a murine sarcoma virus; he presented evidence on the linear map of the double stranded DNA present in Kirsten sarcoma virus transformed cells. Dr. Yahara described experiments in which he used antibodies to tubulin to examine various leukemic cells that had alterations in the cytoskeleton. He hopes these studies will be of clinical usefulness. Dr. Mark Willingham described recent studies on the ultrastructural localization of *src* proteins in cells transformed both by Rous sarcoma virus or by Kirsten sarcoma virus.

In the afternoon session, Dr. Yoshida began the discussion with identification of SFFV-specific sequences coding for a SFFV-specific glycoprotein. Then Dr. Leonard Evans discussed the ribonucleic acids of the defective and nondefective component of Friend anemia and polycythemia viruses. There are prototypes of a new class of retroviral transforming genes. Dr. Ikawa then discussed experiments in his own laboratory on the characterization of the SFFV-specific glycoprotein, gp-55. Dr. Toyoshima described some properties of a newly isolated avian sarcoma virus. Dr. Michael Lai discussed experiments on leukemia specific sequences in avian erythroblastosis virus.

The third day of the meeting was devoted to a special talk by Dr. Wallace Rowe in which he reviewed the current status of the mink cell focus forming virus. This is a very unusual transformation system that may have relevance to human cancer. Finally, Dr. Paul Neiman discussed experiments characterizing malignant lymphomas in chickens induced by avian sarcoma virus. He looked at the organization of the viral sequences in the tumor as the tumor progressed from a small to a large tumor. The rest of this meeting was devoted to general discussion of the meeting and to plans for a possible meeting in the following year.

2) Immunology Area: Biology, Genetics, & Preclinical Immunotherapy

Title: Mechanisms of Host Tumor Immunity and Theoretical Basis for Tumor Immunotherapy (Also see p. 43)

Dates: October 8-10, 1979

Place: Sheraton Maui Hotel, Kaanapali Beach, Maui, Hawaii

Number of Participants:

9 - U.S.

7 - Japanese

Summary:

The first joint seminar of this Immunology Program Area involved presentation and discussion of research in the areas of (1) antigenic nature of tumor cells, (2) fundamental immunologic processes in host responses to tumor, and (3) new approaches and preclinical trials in tumor immunotherapy.

The antigenicity of tumor cells in experimental systems was critically evaluated in presentations which stressed the importance of rigorous identification of tumor-associated antigens. In addition, the relevance of such antigens to tumor sensitivity in immunotherapy was evaluated both in formal presentation and subsequent discussion. Extensive experimentation was reported by both U.S. and Japanese participants in studies of the fundamental immunologic mechanisms of anti-tumor responses. The control of immune responses by specific immuno-regulatory processes was described in a number of tumor systems and new information concerning effector mechanisms mediated by macrophages and natural killer cells was presented. In the final sessions of this meeting, new approaches to tumor immunotherapy were discussed, based upon current experimental findings in areas of basic immunology and tumor immunology. The participating scientists from both Japan and the United States were among the most talented and productive of investigators working in basic immunology, immunogenetics, and tumor biology. This unique opportunity for interaction among these scientists generated not only a valuable exchange of scientific information, but a critical forum for the focussing of basic science perspectives on the development of new approaches to tumor therapy.

3) Diagnosis Area: Automated Cytology & Development of New Techniques

Title: Cytology Automation (Also see p. 47)

Dates: January 27-29, 1980

Place: Sheraton Universal Hotel, Los Angeles, CA, USA

Number of Participants:

12 - U.S.

8 - Japanese

Summary:

The participants assembled informally at a reception in the Hotel on Saturday evening, January 26. The formal meetings began on Sunday morning, January 27. An effort was made to present reports on instrumentation and data analysis techniques the first day, cancer detection systems the second day, and an overview of hematology (leukemia) and other applications the third day. It was the consensus of the participants that the formal presentations and the discussions

that followed had covered the important present applications of automated cytology.

Since the last meeting, there has been progress in the development of sample preparation techniques (Drs. Uei, Kishigami, Wied, Tanaka, and Mendelsohn), in the development and application of automated slide-scanning instrument systems for cervix cancer detection (Drs. Tanaka and Wied), in a promising flow cytometry system for detection of cervix cancer and precancerous lesion (Dr. Tenjin) and in a flow cytometry system for detection of urinary bladder cancer (Dr. Melamed). New slide scanning image analysis techniques were developed for detecting malignant cells within cell clumps based on multispectral measurements (Dr. Noguchi), and for recognizing adenocarcinoma cells in cervico-vaginal smears based on nuclear overlap and inter-nuclear distance as well as more conventional nuclear shape and staining features (Dr. Onoe). A new image sensing device was described for rapid high resolution scanning based on a charge coupled device in linear array composed of 2048 sensor elements (Dr. Takahashi). The role of flow cytomtry in monitoring effects of steroid hormones on DNA, RNA and cell cycle of hormone-sensitive cell lines was described (Dr. Nishiya). The possibility of increasing resolution of cell structure in flow cytometry was discussed following a description of 3-dimensional slit-scanning in flow and tv imaging of cells in flow (Dr. Wheeless). Cell classification by means of cytochemical markers in leukocytes and leukemic cells was reviewed, primarily as applied in flow cytometry (Dr. Ornstein). A new flow cytometric technique was described for sub-classifying acute lymphoblastic and non-lymphoblastic leukemias (and the chronic leukemias) by RNA index, and identifying aneuploid stem-lines by precise DNA measurements (Dr. Andreeff). The present clinical usefulness of this flow cytometry analysis of the leukemias was emphasized, not only for classification but also in following cell kill kinetics, identifying relapse at an early stage and identifying biphasic phenotypic hematopoietic neoplasms that appear to be more common than hitherto believed and may require new treatment strategies. The technology involved in producing monoclonal human antibodies was reviewed, with emphasis on the antibodies to sub-classes of normal leukocytes which will soon be commercially available, and may influence the present classification scheme for leukocytes (Dr. Goldstein). Preliminary experiments with leukemic cells indicate a strong possibility for developing type-specific monoclonal antibodies for classification of leukemias. There was also discussion about the possibility of producing antibodies to carcinoma cells. Data analysis similarities and differences in high resolution scanning systems and flow cytometry systems were described (Dr. Sharpless). The need for computer analysis of large numbers of point measurements in the image of a cell was compared with the analysis of large numbers of cells measured from a specimen analyzed by flow cytometry. The reported results of clinical trials of cervix cancer detection with many different high resolution scanning systems over the last 25 years was reviewed, and steady progress was noted (Dr. Kamentsky). Flow cytometry trials for cervix cancer detection was more recent, and have not yet shown significant improvement. The cost and performance requirements for a successful cervix cancer

detection instrument was calculated, based on various receiver operating curves and reasonable cost estimates of manual and machine methods (Dr. Castleman). It was pointed out that a successful instrument will very likely have to operate far out on the curve, yielding very few false positive results at the expense of many false negative measurements--a conclusion that elicited considerable discussion and surprise. Methods for statistical comparison of machine and human performance were also discussed (Dr. Prewitt). Finally, the broad ranging applications of flow cytometry at Los Alamos (Dr. Mullaney) and at Lawrence Livermore Laboratories (Dr. Mendelsohn) were described, and recent studies at the Battelle Institute using single cell measurements to establish thresholds for distinguishing specific cell types by flow cytometry (Dr. Mullaney). These presentations included a review of the rapid recent progress in automated karyotyping by flow cytometry, analysis of sperm DNA and form changes as a result of toxic chemical or mutagen effect, methods for measuring mutagen effect on other cell types, and new developments in multilaser, multiparameter flow cytometry.

The U.S.-Japan meeting on cytology continue to be extremely productive for participants from both countries, particularly in guiding the direction of research and development as new observations and technology are presented. Therefore it is recommended that the meetings be continued at approximately 12-18 month intervals. It was recommended that the contents of the next meeting, to be held sometime between April 1, 1981, through September 30, 1981, be approximately 50% on cancer detection, diagnosis and monitoring, and approximately 50% on new cancer-related applications of flow cytometry in immunology, cell biology, etc.

B. Exchange of Scientists

1) Kiyoshi Takatsu, Assistant Professor, Department of Oncogenesis, Institute for Cancer Research, Osaka University Medical School, was dispatched to the Scripps Clinic and Research Foundation, for one month from January 7, 1980, and studied the immunobiological property of tumor-associated transplantation antigens in the Department of Molecular Immunology under the supervision of Prof. Ralph A. Reisfeld. Besides, he visited Dr. Martin Dorf in Department of Pathology, Harvard Medical School and Dr. Christopher Henney in Fred Hutchinson Cancer Center to exchange the informations of recent progress in cancer immunology. (Also see p. 51)

2) Dr. Masuo Obinata, Senior Investigator, Laboratory of Viral Oncology, Cancer Institute Tokyo, was dispatched to the Clinical Hematology Branch, National Heart, Blood and Lung Institute in N.I.H., for one month from February 10-March 15, 1980, and studied the switching mechanism of globulin gene expression in mouse fetal development under the supervision of Chief of the Branch, Dr. Arthur W. Nienhuis. On a way of his visiting to the N.I.H., he attended the IVth Annual Symposium on molecular basis of cell-cell interaction at San Diego. During his stay in U.S.A., he also visited Dr. Shigeru Sassa in

Rockefeller Univ., Dr. William E. Hahn in Univ. of Colorado, Medical Center, and Dr. Brian J. McCarthy in University of California at San Francisco, to exchange the information of mechanism of gene expression. (Also see p. 52)

3) Dr. Yoshio Noguchi, Senior Researcher, Information Sciences Division Electrotechnical Laboratory, Tokyo, spent 3 months from November 11, 1979 to February 8, 1980 in National Institute of Health to study the hybrid-system in automated cytology, under the supervision of Dr. Judith Prewitt. During his stay in U.S.A., he visited Dr. Leon L. Wheeless, Stron Memorial Hospital, Univ. of Rochester, Dr. Myron R. Melamed, Memorial Sloan-Kettering Cancer Center and Dr. Ron Jensen, Lawrence Livermore Laboratory to investigate flow-through instrument. (Also see p. 52)

C. Exchange of Materials

Dr. Ichiro Azuma sent the following immuno adjuvants:

2 x 50 mg quinonyl-N-acetylmuramyldipeptide
5 x 100 mg - heat-killed cells of *Propionibacterium acnes*
5 x 100 mg - cell-wall skeleton of *P. acnes*

These samples were distributed to Dr. Ronald Herberman (National Cancer Institute) and Dr. Carl Nathan (Rockefeller University) to examine adjuvant activities on natural killer cells and macrophages. By these examinations, the correlation between the activities for induction of natural killer cells, tumoricidal macrophages and interferon will be delineated.

2. ACCOMPLISHMENTS

The major accomplishments in this first year of the new program area "Cancer Biology, Immunology, and Diagnosis" have concerned exchange of information, reagents, and personnel.

The program in general has become more oriented toward basic science developments and; as a consequence, joint scientific seminars providing maximum opportunity to exchange unpublished information and research ideas have become more important. The principal advisors for the Cellular and Molecular Biology Area, Drs. Ikawa and Pastan, initiated their new program with a stimulating conference on *Src* and *Leuk* Genes; while the advisors for Immunology, Drs. Hamaoka and Hodes, changed the direction of the immunology program and arranged a conference that focussed on new laboratory findings in immunology. Both conferences were quite successful.

The proceedings of a previous conference held under the sponsorship of this program have been published (W.D. Terry and Y. Yamamura (Eds.): *Immunobiology and Immunotherapy of Cancer*. Elsevier North-Holland, New York, NY, 1979, 424 pp.)

While the Immunology and the Cellular & Molecular Biology Areas are concentrating on basic science, the Diagnosis Area continues to provide a forum for joint development of automated cytology techniques.

This very important area has great potential for improving our capacity to detect abnormal cells and has implication for screening, diagnosis, and treatment. Continued development is anticipated, although there are many problems.

3. FUTURE DEVELOPMENTS

The following future plans of the meetings, exchanges of scientists and exchange of reagents are proposed:

1) Cellular & Molecular Biology Area

(a) Meeting: Title; Genetic and Epigenetic Aspects of Cancer
Dates; January 19-21, 1981
Place; Honolulu, Hawaii
Organizer; U.S. - Dr. Ira Pastan
Japan - Dr. Yoji Ikawa

(b) Scientist exchange: Dr. Yoshio Okada, Osaka University
Thema; Cell engineering utilizing cell fusion phenomenon
Period; One month in autumn, 1980
Hosts; Dr. Thomas L. Benjamin, Harvard Medical School
Dr. Frank H. Ruddle, Yale University
Dr. Martin C. Rochsteiner, University of Utah
Dr. Hidesaburo Hanafusa, Rockefeller University

2) Immunology Area: Biology, Genetics & Preclinical Immunotherapy

(a) Meeting: Title; Analysis of the mechanisms for induction of tumor-specific immunity and experimental approach for tumor-immunoprophylaxis and therapy.
Dates; October 20-22, 1980
Place; Osaka, Japan
Organizer; U.S. - Dr. Richard Hodes
Japan - Dr. Toshiyuki Hamaoka

(b) Scientist exchange: Dr. Yoshibumi Ishii, Sapporo Medical College
Thema; Immunological characterization of human tumor-associated antigens as defined by monoclonal antibodies.
Period; September 1-30, 1980
Hosts; Dr. Ralph A. Reisfeld, Scripps Clinic and Research Foundation
Dr. E. A. Boyse, Memorial Sloan-Kettering Cancer Center
Dr. Kyoichi Kano, State University of New York at Buffalo
Thema; Studies on heterophile (Paul-Bunnell) antigen-antibody in Japanese patients with various malignancies.
Period; Six months from mid-December, 1980
Hosts; Dr. Yoshihiko Horiuchi, University of Tokyo
Dr. Haruo Sugano, Cancer Institute

(c) Exchange of reagents: Dr. Ichiro Azuma, Hokkaido University
Research Institute for Immunology
Synthetic muramyldipeptide analogs and derivatives

3) Diagnosis Area: Development of New Techniques

(a) Meeting: Title; Carcinoembryonic Proteins - Cellular and Molecular Biology and Application for Early Diagnosis of Cancer
Dates; December 4-5, 1980
Place; San Diego, USA
Organizer; U.S. - Dr. William H. Fishman, La Jolla Cancer Institute
Japan - Dr. Hidematsu Hirai, Hokkaido University Medical School

(b) Scientist exchange: Dr. Nobuko Ishii, Nagasaki University Medical School
Thema; Radioimmunodetection of hepatocellular carcinoma by antibody to AFP using subtraction method
Period; One month in summer, 1980
Host; Dr. David M. Goldenberg, University of Kentucky College of Medicine

4. SEMINAR AGENDA AND PARTICIPANTS

1) Joint Seminar on "*Src* and *Leuk* Genes"
National Institutes of Health, Bethesda, MD, November 12-14, 1979

AGENDA

November 12, 1979

Structure of Endogenous *src* Protein of CEF	Dr. K. Beemon
Studies on the *src* Proteins of Recovered Avian Sarcoma Viruses	Dr. J. Neil
The Nature of Genetic Interaction which Generates Recombinant Sarcoma Virus in Chickens	Dr. H. Hanafusa
Unusual Features in the Nucleotide Sequence of a cDNA Clone Derived from the Common Region of Avian Sarcoma Virus Messenger RNA	Dr. T. Yamamoto
A New Mutant Derived from ts-NY68	Dr. S. Kawai
Protein Phosphorylation Mediated by the Avian Sarcoma Virus Transforming Gene Product	Dr. R. Erikson
Characterization of p60 *src* Dependent Phosphorylation Products in Cell Free Extracts	Dr. G. Jay
Phosphorylation	Dr. K. Beemon
The Abelson Murine Leukemia Virus Protein is Phosphorylated in vitro to Form Phosphotyrosine	Dr. A. Dasgupta
Protein Phosphorylation in Viral Transformed Cells	Dr. Kin-ichiro Oda
Viral-Chemical Carcinogenesis	Dr. H. Yoshikura

November 13, 1979

The *src* Proteins of Rat-Derived Murine Sarcoma Viruses	Dr. T. Shih
Presence of Linear ds-DNA in KiSV Producers and Its Mapping	Dr. N. Tsuchida
Altered Cytoskeleton in Leukemia Cells	Dr. I. Yahara
Ultrastructural Localization of *src* Proteins	Dr. M. Willingham
Identification of SFFV-specific Sequences coding for SFFV-specific Glycoprotein, gp-55	Dr. M. Yoshida
The RNAs of the Detective and Non-Defective Component of Friend Anemia and Polycythemia Virus Identified and Compared: Prototypes of a New Class of Retroviral Transforming Genes	Dr. L. Evans
Further Characterization of SFFV-specific gp-55	Dr. Y. Ikawa
Some Properties of a Newly Isolated Avian Sarcoma Virus (Y-73)	Dr. K. Toyoshima
Leukemia Specific Sequences in Avian Erythroblastosis Virus	Dr. M. Lai

November 14, 1979

The Current Status of Mink Cell Focus Forming Virus	Dr. W. Rowe
Malignant Lymphomas Induced by Avian Leukosis Viruses	Dr. P. Neiman

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2) Joint Seminar on "Mechanisms of Host Tumor Immunity and Theoretical Basis for Tumor Immunotherapy"
Lahaina Room at the Sheraton-Maui Hotel, October 8-10, 1979

AGENDA

Monday, October 8

(1) ANTIGENIC NATURE OF TUMOR CELLS

Characterization of tumor-associated antigens

8:30 - 9:10 Dr. S. Rosenberg (National Cancer Institute)
"Serologic analysis of human osteosarcoma antigens"

9:10 - 9:50 Dr. Y. Hashimoto (Tohoku Univ. Sch. of Pharmacology)
"Antigen-characteristics of rat bladder cancer and its relevance to immunosensitivity in immunotherapy"

9:50 - 10:15 Dr. D. Meruelo (New York University Medical Center)
"Definition of immune cell surface antigen associated with leukemia"

(2) FUNDAMENTAL IMMUNOLOGIC PROCESS IN HOST RESPONSES TO TUMORS

(a) Mechanisms of macrophage activation and anti-tumor effects

10:30 - 11:15 Dr. T. Tokunaga (National Institute of Health)
"Mode of activation of cytotoxic macrophages"

11:15 - 12:00 Dr. C. Nathan (Rockefeller University)
"Correlation between H_2O_2 release and the ability of macrophages to kill intracellular protozoa and extracellular tumor cells"

(b) Natural killer cell activity and relevance to tumor-resistance

20:00 - 20:45 Dr. K. Okumura (Tokyo Univ. Med. Sch.)
"Surface marker of mouse natural killer cell"

20:45 - 21:30 Dr. R. Herberman (National Cancer Institute)
"Regulation of natural killer cell activity and evidence for role in vivo"

Tuesday, October 9

(c) Regulation of host immune response

8:30 - 9:15 Dr. M. Kripke (Frederick Cancer Research Center)
"Regulation of immunity to UV-radiation-induced skin cancer"

9:15 - 10:00 Dr. S. Fujimoto (Chiba Univ. Med. Sch.)
"Two effector mechanisms against syngeneic tumor in the mouse"

10:30 - 11:15 Dr. M. Greene (Harvard Medical School)
"The cellular basis of the regulation of the immune response to tumor antigen"

11:15 - 12:00 Dr. D. Meruelo (New York University Medical Center)
"H-2D linked mechanism of resistance to radiation leukemia virus"

(3) NEW APPROACHES AND PRECLINICAL TRIALS IN TUMOR IMMUNOTHERAPY

20:00 - 20:45 Dr. T. Kataoka (Japanese Foundation for Cancer Research)
"Lectin-bound murine tumor cell vaccine: Its immunogeneic and immunotherapeutic potency enhanced by immunomodulators"

20:45 - 21:30 Dr. I. Azuma (Hokkaido Univ. Res. Inst. for Immunol.)
"Antitumor activity of quinonyl-N-acetyl-muramyldipeptide derivations"

Wednesday, October 10

8:30 - 9:15 Dr. S. Rosenberg (National Cancer Institute)
"The prolonged growth of cytotoxic T lymphoid cells"

9:15 - 10:00 Dr. T. Hamaoka (Osaka Univ. Med. Sch.)
"Application of T-T cell interaction to tumor immunotherapy"

10:00 - 10:45 Dr. H. Fujiwara (National Cancer Institute)
"The augmentation of in vitro and in vivo tumor-specific T cell-mediated immunity by amplifier T lymphocytes

(4) OPEN DISCUSSION

11:00 - 12:30 "Application of basic tumor immunology studies to the development of new approaches to tumor immunotherapy"

Chairman - Dr. W. Terry (National Cancer Institute)
Japanese Program Leader - Dr. T. Hamaoka (Osaka University)
American Program Leader - Dr. R. Hodes (National Cancer Institute)

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3) Cytology Automation Meeting
Sheraton Universal Hotel, Los Angeles, CA
January 27-29, 1980

AGENDA

Sunday, January 27, 1980	
Welcoming Address and Introductions	Dr. M. Melamed Dr. Y. Tenjin
An Objective Measure of "How Good" is Cytology Automation	Dr. L. Kamensky
Comparison of Data Analysis in Flow and Imaging Systems	Dr. T. Sharpless
Multidimensional Slit-Scan Flow System and Correlation Studies	Dr. L. Wheeless
An Automatic Detection System of Cancer Cells Based on Multispectral Images	Dr. Y. Noguchi
Comparing Human and Machine Performance	Dr. J. Prewitt
Monoclonal Antibodies from Human Hybridomas as Specific Immunocytochemical Cell Markers	Dr. G. Goldstein
Monday, January 28	
Specimen Preparation for Automated Cervical Cancer Cytology	Dr. Y. Uei
Improvement of the Preparation Method of Vaginal Smears for Automated Cytology	Dr. Y. Kishigami
Detection of Uterine Cancer with an Automated Slide Preparation Technique and High Resolution Scanning in 3 Colors Using the Three-Gun Saticon Camera	Dr. G. Wied
Automated Cytological Screening System, Cybest Model 3 and Automated Cell Dispersion and Smearing System	Dr. N. Tanaka
Cost and Performance of Cervical Cancer Prescreening Systems	Dr. K. Castleman
Cytoanalysis by a new system using an Image Sensor	Dr. M. Takahashi
A Study on the Evaluation of the Possibility of Using Flow Cytometry in the First Screening by Automated Cytology	Dr. Y. Tenjin
Regulation of the Cell Cycle by Steroid Hormones in HELA Cells: Flow Cytometric Analysis	Dr. I. Nishiya
Recognition of Adenocarcinoma in Automated Uterine Cytology	Dr. M. Onoe
Flow Cytometry Diagnosis of Carcinoma of the Urinary Bladder	Dr. M. Melamed
Tuesday, January 29	
Use of Cytometry for Classification of Leukocytes and Leukemias with the Technicon Hemalog D	Dr. L. Ornstein

Leukemia Classification and Treatment Monitoring by Flow Cytometry	Dr. M. Andreeff
An Overview of the Los Alamos Scientific Laboratory Program in Flow Cytometry	Dr. P. Mullaney
An Overview of the Analytic Cytology Program in the Biomedical Sciences Division of the Lawrence Livermore Laboratories	Dr. M. Mendelsohn

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5. SUMMARY REPORTS OF EXCHANGE SCIENTISTS

1) KIYOSHI TAKATSU, Department of Oncogenesis, Institute for Cancer Research, Osaka University Medical School
1-1-50 Fukushima, Fukushima-ku, Osaka 553

Host Institution: Prof. Ralph A. Reisfeld, Department of Molecular Immunology, Scripps Clinic & Research Foundation
Dr. Martin E. Dorf, Department of Pathology, Harvard Medical School
Prof. Christopher Henney, Immunology Branch, Fred Hutchinson Cancer Center

Dates of Visit: January 7 through January 11, 1980, Dr. Dorf, Harvard Medical School (Boston)
January 14 through January 26, 1980, Prof. Reisfeld, Scripps Clinic & Research Foundation (La Jolla)
January 29 through February 5, 1980, Prof. Henney, Fred Hutchinson Cancer Center (Seattle)

Summary of Activities:

(1) Exchanging information and discussing about recent progress of tumor immunology and basic immunology with a lot of outstanding scientists was very valuable.
(2) I was given a chance to make a seminar at each institution. This encouraged me and will be helpful for my future work.
(3) I have learned purification methods of tumor associated transplantation antigens (TSTA) including other surface protein.
(4) I have carried out isolation and characterization of tumor surface antigens.

Overall Assessment of the Program:

(1) The program assisted in achieving my research objectives.
   a. Learning basic methods how to handle membrane surface protein including TSTA.
   b. Exchanging informations.
   c. Very valuable alloantisera such as anti-Lyt, anti-Ia, anti-HLA and anti-Qa-1 antisera were given by Dr. Greene, Dr. Ferrone and Dr. Stanton, respectively.
(2) I plan to continue my collaborative work with several peoples; exchanging samples and discussing each other about results with respect to soluble mediators which is required for primary in vitro induction of killer T cells
(3) I think that my efforts have contributed to the progress of the NCI-Japan Cancer Program in the following points;
   a) exchanged information concerned about applicability of immunotherapy model employing immunization of PPD-coated tumor cells to cancer patients.
   b) will make a collaborative work including sample exchange.

2) MASUO OBINATA, Cancer Institute, Dept. of Viral Oncology
1-37-1 Kami-ikebukuro, Toshima-ku, Tokyo 170, JAPAN

Host Institution: Dr. Arthur W. Nienhuis, Chief, Clinical Hematology Branch, National Heart, Lung, and Blood Institute, National Institute of Health, Bethesda, Md 20014 U.S.A.

Dates of Visit: Feb. 11-14, San Diego, The 4th Annual Symposium on the Molecular Basis of Cell-Cell Interaction
Feb. 15-Mar. 7, Dr. A. W. Nienhuis, (N.I.H.)
Mar. 8, Dr. S. Sassa, (Rockefeller University)
Mar. 11, Dr. W. E. Hahn, (University of Colorado)
Mar. 12-14, Dr. B. J. McCarthy, (University of California, San Francisco, Medical Center)

Summary of Activities:

We have coordinated to examine the active and inactive conformation of specific genes in chromatin by means of selective digestion by deoxyribonuclease I. This method can be applied to several differentiated and cancer cells to determine the characterization of cells.

In Dr. Nienhuis' laboratory, it has been reported that DNase I selectively digested the actively transcribed adult β-globin genes as well as the potentially active fetal γ-globin genes in chromatin from sheep erythroblast cells.

In our laboratory in Japan, we have cloned mouse fetal *y*-globin gene and studied on the expression of this gene in cultured Friend leukemia cells, showing that *y*-globin gene does not express in this cell.

We wanted to examine whether fetal *y*-globin gene is active in its chromatin conformation in Friend leukemia cells by DNase I digestion.

During my visit to Dr. Nienhuis' laboratory, with collaboration with Dr. R. Croissant, we developed more sensitive method for the DNase I digestion of specific globin genes by Southern's blotting technique.

In Japan, I will continue to apply this sensitive method to cultured Friend leukemia cells using *y*-globin gene probe.

3) YOSHIO NOGUCHI, Information Sciences Division, Electrotechnical Laboratory, Agency of Industrial Science and Technology, M.I.T.I.
1-1-4, Umezono, Sakura-mura, Ibaraki-ken 〒305

Host Institution: Judith M. S. Prewitt, Ph.D., Division of Computer Research and Technology National Institutes of Health

Dates of Visit: From November 11, 1979 till February 9, 1980 (91 days)

Summary of Activities:

The subject of research is a study for hybrid-system in automated cytology. Before the study, I had to learn and inspect various types of instruments for flow cytometry, since Japanese researchers are acquainted with the instruments fabricated based on image processing system but not familiar with that based on flow-through system. To fulfill the aim, I studied at NIH and made technical visits to the Biomedical Sciences Division of Lawrence Livermore Laboratory (Livermore, CA.), the Division of Bio-Physics & Instrumentation of Los Alamos Scientific Laboratory (Los Alamos, New Mexico), Department of Pathology of University of Rochester (Rochester, NY.) and the Department of Pathology of Memorial Hospital for Cancer and Allied Diseases (New York, NY.). I also visited Coulter Electronics Inc. (Concord, MA.), Ortho Instruments (Westwood, MA.) and Becton Dickinson FACS System (Sunnyvale, CA.). I participated in the US-Japan Seminar for Automated Cytology (at Los Angeles, CA.) and Engineering Foundation Conference on Automated Cytology VII (at Asilomar, Pacific Grove, CA.), and introduced one of my studies for automated cytology.

I learned enough knowledge and technological considerations which might be sufficient to fabricate a laser flow cytometer. I recognized that one kind of the hybrid systems had been fabricated at Rochester University. They are called the swept slit image correlation system and the X-Y-Z slit-scan system.

At NIH, I discussed with Dr. Judith Prewitt about several techniques on image processing for automated cytology. They had also compared various techniques used in flow cytometry and in computer processing of biomedical image. On image processing, I discussed with Prof. G. L. Wied, University of Chicago (Chicago, Ill.) and Dr. K. Castleman, Jet Propulsion Laboratory (Pasadena, CA.), about technical problems lying in the research for automated cytology, especially, about utilizations of color images and statistical evaluation method of cyto-prescreener. On laser flow cytometer, I learned mechanisms of the dual beam system, the scatter-light analysis system, the slit-scan system and basic scheme at Lawrence Livermore Laboratory, Los Alamos Scientific Laboratory, Rochester University and Memorial Hospital for Cancer and Allied Diseases, respectively. I evaluated jet-in-air system at Becton Dickinson and closed system at Ortho Instruments. I gained in knowledge of various kinds of research fields, fluorescence energy transfer theory and historical achievements in flow cytometry during the days of the Conference and the seminar.

Judging from the prospective broad application and future of the flow cytometry, it is indispensable to fabricate a laser flow cytometer by Japanese technology for sound progress in such researches in Japan. The gained knowledge in the area and further collaboration with the American scientists will help Japan when it is possible to start to develop a new laser flow cytometer.

BEST DOCUMENT AVAILABLE

III. TREATMENT AREA

III. TREATMENT AREA

Program Coordinators: Dr. Stephen K. Carter, U.S.A.
Dr. Yoshio Sakurai, Japan

Principal Advisors:

U.S.A.: Dr. John D. Douros
Dr. Abraham Goldin
Dr. Franco M. Muggia
Dr. Steven Rosenberg
Dr. Glenn E. Sheline

Japan: Dr. Shoji Hattori
Dr. Hiroki Koyama
Dr. Yoichiro Umegaki
Dr. Makoto Ogawa

1. ADMINISTRATIVE REPORT

A. Seminars

1) Seminar on New Drugs under Clinical Evaluation and Their Application in Treatment of Solid Tumors: 1979 U.S.-Japan, 5th Annual Program Review of Treatment Area (Also see p. 59)
San Francisco, U.S.A. May 21-23, 1979
Organizers: S.K. Carter; Y. Sakurai
Participants: 18 from U.S.A.; 10 from Japan

2) Seminar on High LET and Allied Areas in Radiotherapy (Also see p. 64)
Kyoto, Japan May 22-23, 1979
Organizers: A. Tsuya; G.E. Sheline
Participants: 17 from U.S.A.; 36 from Japan

3) Seminar on Treatment of Lung Cancer by Chemotherapy Combined with Other Modality (Also see p. 71)
Osaka, Japan January 28-30, 1980
Organizers: S. Hattori; S.K. Carter
Participants: 9 from U.S.A.; 10 from Japan

B. Exchange of Scientists

1)~3) E.A. KNAPP, M.D., Director, LAMPF, Los Alamos, New Mexico, J.R. CASTRO, Professor, Berkeley Lab., Univ. of Calif., Berkeley, and M. GOITEIN, Ph.D., Harvard Medical School, Philadelphia, visited Japan in May 1979 to set up the cooperative program of high LET radiotherapy between the both countries. (Also see p. 76)

4) NOBORU HORIKOSHI, M.D., Section Chief, Department of Clinical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, was dispatched to the University of Texas System Cancer Center, Houston, Texas, for one month from November 4, 1979, and studied the system of acceptance of breast cancer patients and also diagnosis and treatment at the Medical Breast Service in the M.D. Anderson Hospital under the supervision of Dr. Emil J. Freireich. Besides, he visited San Francisco to see Drs. S.K. Carter and M. Friedman to inspect the activities of Northern California Oncology Group. (Also see p. 77)

C. Exchange of Materials

A vigorous exchange of chemicals has been carried out. The data of screening, as well as some number of compounds themselves, were put into the screening program of NCI, USA, and also several cancer drugs of interest in Phase I and II were sent from NCI to Japanese clinical investigators by mediation of the Japanese coordinator's office.

2. SUMMARY OF ACTIVITIES

Chemotherapy is now climbing up a steep slope with difficulty, though we have achieved fairly good success in treatment of hematologic malignancies. To expand the success definitely to the treatment of solid cancers, we must seek for rational and effective combination of various treatment modalities.

The principal objectives of the program area of treatment in the second five year period are to develop new antitumor drugs, new development in radiation oncology, new immunotherapeutic approaches, and combined modality studies most appropriate to specific disease sites. Disease sites to be emphasized include gastric cancer, lung cancer, breast cancer and bladder cancer.

Through the term of 1979 FY, a cooperative clinical trial in patients with advanced gastric cancer, employing the protocols common to both countries, was initiated, which has extensively promoted a mutual comprehension between the United States and Japan in the practice, analysis, and evaluation of clinical data in order to establish future cooperative studies in the treatment of cancers cited above.

3. REPORTS ON SEMINARS

One of the activities, which has been continued from the start of cooperative program in 1974, is the collaborative work in evaluating the analogs of nitrosourea, fluorinated pyrimidine, anthracycline, bleomycin, protease inhibitor, and others. A comparative study in evaluation of the analogs needs much effort and time, that will be greatly saved through utual discussions and collaborative studies through the seminars. The other important purpose of the seminars is to find the better treatment protocols with combination of drugs, or with combined modalities of treatment, for solid cancer patients. The experience in Japan of the surgical adjuvant studies with a great number of patients of gastric cancer was brought up for discussion with the U.S. participants with interest.

Lung cancer was considered for intensive discussion in the third seminar of the year, held in January, 1980, entitled "Treatment of Lung Cancer by Chemotherapy Combined with Other Modality." This seminar was excellently organized by Dr. Shoji Hattori, a Principal Advisor of Treatment Area of this Program, as a continuation of the seminar held from January 31 to February 2, 1979, in Miami organized by Dr. Y. Yamamura and Dr. Selawry.

In this seminar, Dr. Carter emphasized that since the efficacy of treatment of lung cancer would be varied, according to the histological

type, stage of disease, age, race, or host condition of patients, the clinical study with a large number of patients and on an international scale is of importance. As for the chemotherapy of lung cancer, Dr. Friedman's report on treatment with VAM (VP16-213, Adriamycin, Methotrexate) attracted interest among the participants. He stated that the median survival time of the treated patients with limited disease was indicated to be 488 days.

From Japanese side, Dr. Hattori summarized the clinical data of 373 cases of non-resected adenocarcinoma in Japan, mostly treated with a combination protocol consisting of mitomycin C, 5-FU, and Ara-C (MFC), which have been put in the national registry. Dr. Yasumoto presented the result of immunotherapy of lung cancer with BCG-CWS and Nocardia-CWS. He reported that the 5-year survival curve of 169 patients in the stage III and IV, treated with BCG-CWS, was significantly better, when compared with 210 cases of historical control. On the other hand, Dr. Salyer and Dr. Shimosato discussed the histology of lung cancer in detail, and the presentation of the former was a good reference for Japanese participants.

A seminar entitled "High LET and Allied Area in Radiology" was held on May 22-23, 1979, in Kyoto, which was organized by Dr. Tsuya and Dr. Sheline, and planned as a continuation program of the Radiotherapy Area in the first 5 year period of this Program. The seminar included discussions on accelerator design, particle physics, radiation biology and radiation therapy. It was successful in establishing a cooperation program between both countries in this new area of fundamental research for cancer treatment.

4. REPORT ON EXCHANGE OF SCIENTISTS

Dispatch of 3 American scientists to Japan, who were experts in proton radiation therapy, was very helpful for the Japanese side, because the research in this field is still in the beginning stages in Japan and there is a lot of technolcgy developed in the United States. The future cooperation in this field through this program will be greatly profitable for both countries, especially for Japan.

A clinical doctor of Cancer Institute Hospital, Noboru Horikoshi, M.D., was sent to the University of Texas System Cancer Center in Houston. He visited Medical Breast Service in M.D. Anderson Hospital to learn how the breast cancer patients are accepted, diagnosed, and treated by a cooperative team of surgeons, radiologists, and clinical oncologists in this Hospital. It was very useful, because presently in Japan breast cancer patients are mostly accepted and treated in the department of surgery of hospital.

5. PLANS FOR FUTURE MEETINGS

Through the business meetings held during the 1979 fiscal year, the following meetings are being planned.

1) Seminar on Development and Evaluation of Cancer Treatment.
   (Seminar of U.S.-Japan 6th Annual Program Review of Treatment Area, in which development of chemotherapy in combined modality of treatment will be discussed.)
   Date: June 7-9, 1980
   Location: Tokyo, Japan
   Organizers: Y. Sakurai; S.K. Carter
2) Seminar on High LET Radiations and Combined Modalities.
   Date: November 10-12, 1980
   Location: Hawaii, U.S.A.
   Organizers: G.E. Sheline; Y. Umegaki
3) Seminar on Treatment of Breast Cancer
   Date: Unspecified (Late 1980 FY)
   Location: San Antonio, Texas, USA
   Organizers: William L. McGuire; Hiroki Koyama

6. FUTURE PROGRAM DEVELOPMENT

Having succeeded in cooperation in treatment of gastric cancer and lung cancer, plans are being made to extend the program to establish collaborative research on treatment of breast cancer in 1980 fiscal year. In this plan, chemotherapy combined with other modalities of treatment, and also the problem of hormone receptors and hormone therapy, will be the most interesting items for discussions. The difference in prognosis and hormone-dependency of the breast cancer among patients in the United States and Japan will also be a focus of investigation. The seminars on treatment of bladder cancer, and immunotherapy will be followed in 1981 FY.

The development of new treatment modalities and new drugs in Phase I and II studies will be reviewed and discussed, which is an important activity to maintain continuity in this area of the program.

7. SEMINAR AGENDA AND PARTICIPANTS

1) 1979 U.S.-JAPAN ANNUAL PROGRAM REVIEW: New Drugs under Clinical Evaluation and Their Application in Treatment of Solid Tumors

Sheraton-Palace Hotel, Market & New Montgomery
San Francisco (Regency Room), May 21-22, 1979

AGENDA

May 21

8:30	Welcome and Introduction	Dr. Stephen K. Carter
I. Anthracyclines		
Chairman:	Dr. Abraham Goldin	
8:40	Current Status of Studies with AD-32	Dr. Ronald Blum
8:55	Current Status of U.S. Studies with Carminomycin	Dr. Robert Comis
9:05	Current Status of Japanese Studies with Aclacinomycin-A	Dr. Toshikazu Oki
9:20	Overview of the NCI Anthracycline Program	Dr. Nicholas Bachur
9:40	An Overview of the Anthracycline Cardiac Toxicity Studies Program at Stanford	Dr. John Daniels
10:00-10:15	Discussion	
10:15-10:30	Coffee Break	
II. Bleomycins		
Chairman:	Dr. Hamao Umezawa	
10:30	Current Status of PEP Bleomycin Studies in Japan	Dr. Shigeo Ikeda
10:50	Tallysomycin Studies in the U.S.	Dr. Stanley Crooke
11:05	Discussion	
III. Fluorinated Pyrimidines		
Chairman:	Dr. Michael Friedman	
11:20	Status of New Fluorinated Pyrimidine Analogues in Japan	Prof. Yoshio Sakurai
11:40	U.S. Studies on the Pharmacology of Ftorafur	Dr. Wolfgang Sadee
12:00-12:30	Discussion	
12:15- 2:15	LUNCH	
IV. Nitrosoureas		
Chairman:	Prof. Yoshio Sakurai	
2:20	Current Status of GANU and Other Nitrosoureas in Japan	Dr. Makoto Ogawa
2:40	PCNU Studies in the Northern California Oncology Group	Dr. Michael Friedman
2:55	The Experimental Rationale for New Nitrosourea Development	Dr. Kurt Kohn
3:15- 3:30	Discussion	
3:30- 3:45	Coffee Break	

V. Other New Drugs

Chairman: Dr. Stephen K. Carter

3:45	New Natural Products in Development	Dr. John Douros
4:00	The Current NCI Screening Approach and Its Status	Dr. Abraham Goldin
4:20	New Drugs in Phase I Study in the U.S.	Dr. Franco Muggia
4:40	Bestatin Studies in Japan	Dr. Hamao Umezawa
5:00	A Review of Clinical Studies on Bestatin	Dr. Sutemi Oka
5:10	N^4-Behenoyl-Cytosine Arabinoside Studies in Japan	Dr. Kazumasa Yamada
5:30- 5:45	Discussion	
6:30	DINNER FOR PARTICIPANTS	

May 22

I. Gastric Cancer

Chairman: Dr. Franco Muggia

8:30	Current Status of U.S. Studies with Chlorozotocin	Dr. Philip Schein
9:10	Current Status of FAM Studies	Dr. Philip Schein
9:25	Surgical Adjuvant Studies in the U.S.	Dr. George Higgins
9:40	The NCOG-Japanese Gastric Cancer Study	Dr. Michael Friedman and Dr. Makoto Ogawa
10:00-10:15	Discussion	
10:15-10:30	Coffee Break	

II. Oat Cell Lung Cancer

Chairman: Dr. Hugh Davis

10:30	Oat Cell Lung Studies in Japan	Dr. Harumichi Ikegami
10:50	The Development of Non-cross resistant Combinations	Dr. Oleg Selawry
11:10	The NCOG Study Comparing POCC vs. VAM	Dr. John Daniels
11:30	Combined Modality Studies in the U.S.: An Overview	Dr. Robert Livingston
11:55-12:15	Discussion	
12:15- 2:00	LUNCH	

III. Head and Neck Cancer

Chairman: Dr. Makoto Ogawa

2:00	Combination Chemotherapy of Head and Neck Cancer in U.S.	Dr. Robert Wittes
2:20	Platinum plus Methotrexate	Dr. Charlotte Jacobs
2:40- 3:00	Discussion	
3:00- 3:15	Coffee Break	

IV. Breast Cancer

Chairman: Dr. Philip Schein

3:30	Current Status of Chemotherapy in Advanced Disease in the U.S.	Dr. Hugh Davis
4:00	Current Status of Chemotherapy in Advanced Disease in Japan	Dr. Tomio Wada

4:20	Adjuvant Chemotherapy - Where We are Today	Dr. Stephen K. Carter
4:45- 5:00	Discussion	

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2) Seminar on "High LET and Allied Areas in Radiotherapy"
Kyoto, Japan, May 22-23, 1979

AGENDA

May 22, 1979

8:10 Opening Remarks - Glenn E. Sheline, Ph.D., M.D. and Akira Tsuya, M.D. Radiation Therapy Program Coordinators

I. HIGH LET

A. Accelerator Design — Moderators: M. Goitein & T. Fukumoto

8:15	Y. Hirao	Institute for Nuclear Study, Tokyo Univ.	Design of heavy ion accelerator for medical use
8:30	K. Tsukada	Institute for Nuclear Energy, Nippon Univ.	Negative-pion production by electrons from thick nuclear targets at immediate energies
8:35	E. Knapp	Los Alamos Sci. Lab. Univ. of California	PIGMI-pion generator for medical irradiation

B. Particle Physics — Moderators: M. Goitein & Y. Hirao

8:55	A. Smith	Los Alamos Sci. Lab. Univ. of California	Characterization of pion therapy beam at LAMPF
9:15	C. Tobias	Donner Lab., Univ. of California, Berkeley	Radiobiological physics of heavy-ion beams
9:35	T. Inada	Div. of Clin. Res. Tsukuba Univ.	Proton field shaping by spot scanning
9:55	A. Ito	Cyclotron Unit, Inst. of Medical Sci. (IMS), Tokyo Univ.	Microdosimetry of high LET therapeutic beam

10:15 Break for Coffee (15 mins.)

C. Biology — Moderators: T. Phillips & K. Sakamoto

10:30	K. Sakamoto	Dept. of Rad. Biophys. Tokyo Univ.	Biological basis of high LET radiation therapy
10:50	H. Ohara	Div. of Physiol. and Path., Natl. Inst. of Rad. Sci. (NIRS)	Biological effectiveness of the NIRS cyclotron produced neutron beams for radiotherapy
11:10	E. Hall	Dept. of Radiol. Columbia Univ.	Update of neutron radiation biology
11:30	M. Raju	Los Alamos Sci. Lab. Univ. of California	Radiobiology of heavy ions
11:50		LUNCH	
1:00	T. Phillips	Dept. of Rad. Oncol., Univ. of California, SF	The RBE as a function of fraction size for heavy particles
1:20	M. Raju	Los Alamos Sci. Lab. Univ. of California	Radiobiology of pions

D. Treatment Planning — Moderators: T. Phillips & T. Inada

1:40	A. Smith	Cancer Research and Treatment Center, Univ. of New Mexico	Treatment planning for pion therapy patient at LAMPF

2:00	K. Kawachi	Div. of Physics, Natl. Inst. of Radiol. Sci.	NIRS proton therapy facility
2:20	M. Goitein	Dept. of Rad. Med. Harvard Med. Sch.	Treatment planning with proton beams with special emphasis on the use of computed tomography
2:40	J. Castro	Saroni Tumor Inst. of Mount Zion Hosp. and Lawrence Berkeley Lab. of the Univ. of California, Berkeley	An update on treatment planning for heavy-ion therapy
3:00	Break for Coffee (15 mins.)		

E. Therapy — Moderators: H. Suit & Y. Umegaki

3:15	H. Tsunemoto	Div. of Clin. Res. Natl. Inst. of Radiol. Sci.	Results of clinical trial with 30 MeV d_1-Be neutrons at NIRS
3:35	Y. Iino	Dept. of Radiol., IMS, Tokyo Univ.	Fast neutron therapy at IMS
3:55	S. Kramer	Dept. of Rad. Therapy & Nucl. Med., Thomas Jefferson Univ. Hosp.	Update on clin. neutron trials in the U.S.
4:15	S. Morita	Div. of Clin. Res. Natl. Inst. of Radiol. Sci.	Fast neutron therapy for squamous cell carcinoma and adenocarcinoma of the uterine cervix
4:35	Y. Honke	Div. of Hosp., Natl. Inst. of Radiol. Sci.	Fast neutron therapy for carcinoma of the prostate and urinary bladder
4:55	Adjourn		
7:00 to 9:00		RECEPTION AT "CHAGETSU"	

May 23, 1979

Moderators: Y. Umegaki & H. Suit

8:15	J. Castro	Saroni Tumor Inst. of Mount Zion Hosp. and Lawrence Berkeley Lab. of the Univ. of California, Berkeley	Current status of clinical particle radiotherapy at Lawrence Berkeley Laboratory
8:35	M. Kligerman	Cancer Res. & Treatment Center, Univ. of New Mexico	Current observations of pion radiation therapy at LAMPF
8:55	M. Goitein	Dept. of Radiation Medicine, Harvard Medical School	Implementation of fractionated proton radiation therapy at the Harvard Cyclotron Laboratory
9:15	H. Suit	Dept. of Radiation Medicine, Harvard Medical School	Clinical evaluation of fractionated proton beam therapy in human cancer patients

II. HYPOXIC CELL SENSITIZERS, HYPERTHERMIA AND RADIOPROTECTORS

Moderators: E. Hall and M. Abe

1:20	T. Sugahara	Dept. of Fundamental Radiology, Kyoto Univ.	Biological basis of cell sensitizers for radiation therapy
4:45	T. Phillips	Dept. of Radiation Oncology, Univ. of California, SF	Phase I-II clinical studies of the hypoxic cell sensitizer misonidazole in the RTOG
10:00	Y. Onoyama & K. Masuda	Dept. of Radiology Kawasaki Med. Col. and Kyushu Univ. Hosp.	Radiosensitization by misonidazole in animal tumor and prospects of its clinical trial in Japan
10:20	E. Hall	Dept. of Radiology Columbia University	Cytotoxicity of hypoxic cell sensitizers

Break for Coffee (15 mins.)

11:00	T. Phillips	Dept. of Radiation Oncology, Univ. of California, SF	The biological basis and clinical potential of sulfhydryl radioprotectors
11:35	K. Tanaka	Dept. of Radiology, Tenri Hospital	Protective effect of WR-2721
11:45	G.E. Adams	Inst. for Cancer Research, U.K.	Hypoxic cell sensitizer
12:00	R. Johnson	Dept. of Radiation Medicine, Roswell Park Memorial Hosp.	Hyperthermia and radiation therapy

LUNCH

F. High LET Late Damage Moderators: J. Castro & H. Tsunemoto

1:40	S. Kramer	Dept. of Radiation Therapy and Nuclear Medicine, Thomas Jefferson Univ. Hosp.	Complications of particle radiotherapy; the RTOG registry and development of a scoring system
2:00	Y. Umegaki	formerly head of Div. of Clin. Res. NIRS	Modification of NSD and TDF for the assessment of the figure of merits in radiation therapy

III. INTRAOPERATIVE RADIOTHERAPY

Moderators: J. Castro & M. Abe

2:20	M. Abe	Dept. of Radiology Kyoto Univ. Hosp.	Intraoperative therapy for malignant disease in Japan
2:40	H. Suit	Dept. of Radiation Medicine, Harvard Medical School	Intraoperative electron beam radiation therapy
3:00	M. Odaka	Dept. of Surgery Chiba Univ. Hosp.	Intraoperative therapy for carcinoma of the stomach

Break for Coffee (15 mins.)

3:30	T. Matsuda	Dept. of Radiotherapy Metropolitan Komagome Hospital	Clinical experience of intraoperative radiotherapy for pancreatic cancer and brain tumors
3:50	K. Todoroki	Div. of Clin. Res. Tsukuba Univ.	Intraoperative radiotherapy of biliary duct carcinoma

IV. DIAGNOSTIC APPLICATIONS OF PARTICLES

Moderators: M. Goitein & T. Inada

4:10	C. Tobias	Lawrence Berkeley Lab. Univ. of California Berkeley	Heavy ion radiography with comments by M. Goitein
4:35	Closing Remarks		
4:45	Adjourn		

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3) JOINT LUNG CANCER SEMINAR

International Hotel, Osaka, January 28-30, 1980

AGENDA

January 28 (Monday)

13:00 Opening Remarks Dr. S. Hattori (Organizer)
Dr. Y. Yamamura (Steering Comm.)

13:10 I. INTRODUCTION (Chairman: Dr. Y. Sakurai)
Multidisciplinary opportunities in the treatment of bronchogenic carcinoma. Dr. S. K. Carter
(20 min.)
Discussion (10 min.)

13:40 II. EXPERIMENTAL MODELS AND NEW DRUGS
Moderators: Dr. S. K. Carter and Dr. Y. Yamamura

1. Experimental models for predictive drug effects in lung cancer. Dr. A. Goldin
(20 min.)
Discussion (10 min.)

14:10 2. Lung metastasis in mice - experimental models and chemotherapy. Dr. T. Tsuruo
(20 min.)
Discussion (10 min.)

14:40 3. New synthetic immunopotentiating agents and their antitumor activities. Dr. Y. Yamamura
(20 min.)
Discussion (10 min.)

15:10 - 15:30 Coffee Break (20 min.)

15:30 Moderators: Dr. A. Goldin and Dr. S. Hattori

4. New drugs of interest and old drugs of renewed - Interest in cancer chemotherapy. Dr. J. Macdonald
(20 min.)
Discussion (10 min.)

16:00 5. An overview of combination chemotherapy studies in Japan. Dr. M. Ogawa
(20 min.)
Discussion (10 min.)

16:30 6. Combination chemotherapy of metastatic non-small cell lung cancer. Dr. J. Macdonald
(20 min.)
Discussion (10 min.)

17:00 - 17:30
Discussion on chemotherapy and experimental models
(Modulators: Dr. S. K. Carter and Dr. Y. Sakurai)

17:30 Adjourn

19:00 - 21:00 Reception (Buffet style) at International Hotel, Osaka All attendants

January 29 (Tuesday)

9:00 III. IMMUNOTHERAPY

Moderators: Dr. W. R. Salyer and Dr. Y. Hayata

1. Non-specific adjuvant immunotherapy of lung cancer with BCG-CWS and Nocardia-CWS. Dr. K. Yasumoto
   (20 min.)
   Discussion (10 min.)

9:30 2. Surgical adjuvant immunotherapy of lung cancer Dr. E. C. Holmes
   (20 min.)
   Discussion (10 min.)

10:00 - 10:20 Break (20 min.)

10:20 Moderators: Dr. E. C. Holmes and Dr. K. Yasumoto

3. Experimental lung cancer and its application to clinical model. Dr. M. Yoshimoto
   (20 min.)
   Discussion (10 min.)

10:50 4. New developments in immunotherapy - Intralesional BCG. Dr. E. C. Holmes
   (20 min.)
   Discussion (10 min.)

11:20 - 11:50
Discussion on immunotherapy
(Modulators: Dr. E. C. Holmes and Dr. K. Yasumoto)

12:00 - 13:00 Lunch

13:10 IV. OAT-CELL CARCINOMA AND MULTIDISCIPLINARY OPPORTUNITY

Moderators: Dr. J. Macdonald and Dr. M. Ogawa

1. Overview of current oat-cell carcinoma studies in the United States. Dr. P. Bunn
   (20 min.)
   Discussion (10 min.)

13:40 2. Combined modality therapy of small cell carcinoma in Japan. Dr. S. Hattori
   (20 min.)
   Discussion (10 min.)

14:10 3. A Phase III trial of an alternating VS. A sequential multidrug chemotherapy program for oat-cell cancer - An NCOG study. Dr. M. Friedman
   (20 min.)
   Discussion (10 min.)

14:40 - 15:00 Coffee Break (20 min.)

15:00 Moderators: Dr. H. G. Seydel and Dr. T. Kitagawa

4. Clinical results of combined radiotherapy and chemotherapy. Dr. T. Kitagawa
   (20 min.)
   Discussion (10 min.)

15:30 5. Radiation therapy of oat-cell lung cancer - Current status and new developments. Dr. H. G. Seydel
   (20 min.)
   Discussion (10 min.)

16:00 Moderators: Dr. M. Friedman and Dr. S. Hattori

6. Small cell lung carcinoma - Histologic sub-typing. Dr. W. R. Salyer
   (20 min.)
   Discussion (10 min.)

16:30 7. Morphologic aspects of cases with small cell carcinoma which survived over 30 months. Dr. Y. Shimosato
   (20 min.)
   Discussion (10 min.)

17:00 - 17:30 Discussion concerning oat-cell lung cancer
(Modulators: Dr. M. Friedman and Dr. S. Hattori)

17:30 Adjourn

19:00 - 21:00 Dinner at Restaurant Alaska (Invited Speakers) (Invited Guests)

January 30 (Wednesday)

9:00 V. NON-OAT CELL CARCINOMA AND MULTIDISCIPLINARY OPPORTUNITY

Moderators: Dr. P. Bunn and Dr. Y. Shimosato

1. Chemotherapy adjuvant trials in resectable disease. Dr. C. Mountain
   (20 min.)
   Discussion (10 min.)

9:30 2. Chemotherapy of advanced non-oat cell carcinoma of the lung - In relation to combined therapeutic modalities. (20 min.) Dr. Y. Hayata
   Discussion (10 min.)

10:00 - 10:20 Coffee Break

Moderators: Dr. C. Mountain and Dr. Y. Hayata

10:20 3. Current approaches to radiation therapy in non-oat cell lung cancer Dr. H. G. Seydel
   (20 min.)
   Discussion (10 min.)

10:50 4. The staging of bronchogenic carcinoma and its impact on clinical trials. Dr. C. Mountain
   (20 min.)
   Discussion (10 min.)

11:20 - 11:50 Discussion concerning non-oat cell lung cancer
(Modulators: Dr. C. Mountain and Dr. Y. Shimosato)

11:50 - 12:10
SUMMARY AND CLOSING REMARKS
Dr. S. K. Carter (Coordinator)
Dr. Y. Sakurai (Coordinator)

12:10 - 13:00 Lunch

13:00 Adjourn

13:00 - 15:00 BUSINESS MEETING
Members of Steering Comm.

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Mr. Barron
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8. SUMMARY REPORTS OF EXCHANGE SCIENTISTS

1) EDWARD A. KNAPP, PH.D., Los Alamos Scientific Laboratory
University of California, Los Alamos
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Host Institution: Dr. Kineo Tsukada, Japan Atomic Energy Research Institute

Dates of Visit: May 21-31, 1979

Summary of Activities:

Attended the US-Japan Meeting on radiation oncology in Kyoto, Japan. Also visited the Japan Atomic Energy Research Institute to discuss high energy particle physics and the application of accelerator-produced radiation to applied physics and medical needs. Discussions were part of the on-going joint collaboration on high energy particle radiation.

2) JOSEPH R. CASTRO, M.D., Department of Radiation Oncology, Mount Zion Hospital and Medical Center, San Francisco, California

Host Institution: Dr. T. Arai and Dr. S. Morita, Hospital Radiotherapy Department, National Institute of Radiological Science, Chiba, Japan

Dates of Visit: May 21-31, 1979

Summary of Activities:

Visited NIRS in Chiba with Dr. Michael Goitein to discuss the high energy (neutron and photon beam) radiation therapy of patients with cervical cancer. Also they observed several patients under treatment. The problems of staging, treatment and follow-up were extensively discussed for comparability studies. Collaboration on high energy radiation therapy will be continued in the future. Also attended the US-Japan meeting on radiation oncology in Kyoto.

3) MICHAEL GOITEIN, PH.D., Department of Radiation Medicine, Massachusetts General Hospital, Boston, Massachusetts

Host Institution: Dr. T. Arai and Dr. S. Morita, National Institute of Radiological Sciences, Chiba, Japan

Dates of Visit: May 21-31, 1979

Summary of Activities:

Accompanied Dr. Joseph Castro on visits to the Hospital Radiotherapy Department of NIRS. See report on Dr. Castro.

4) NOBORU HORIKOSHI, M.D., Department of Clinical Oncology, Cancer Institute Hospital, Division of Clinical Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research

The object of my visit to the United States, from November 4 to December 3, 1979, was to investigate the systems of diagnosis and treatment of breast cancer. Four main active institutions, in the field of treatment and research of breast cancer were selected for this purpose.

(1) M.D. Anderson Hospital and Tumor Institute
Dr. Emil J. Freireich
Head, Dept. of Developmental Therapeutics
Dr. George R. Blumenschein
Chief, Medical Breast Clinic
Dept. of Medicine

(2) University of Wisconsin
Dr. Paul P. Carbone
Director, Wisconsin Clinical Cancer Center
Head, Dept. of Human Oncology

(3) University of California, San Francisco
Dr. Michael A. Friedman
Cancer Research Institute

(4) Stanford University
Dr. Stephen K. Carter
Director
Northern California Cancer Program

At each institution, I could see treatment and care of in- and out-patients. It was interesting and useful for us to know such a system as "Breast Planning Clinic", held in M.D. Anderson Hospital, for better management.

There were several new protocols for us: treatment of breast cancer patient in PEPA, and continuous intravenous treatment with a special catheter using drugs such as adriamycin, vinblastine, bleomycin and MMC.

There are standard combination chemotherapy for breast cancer: ACF at M.D. Anderson Hospital and CMFP in the ECOG. But we still need active drugs for this disease. Protocols and information were obtained about phase II drugs for breast cancer, which are not tried yet in Japan, such as mAMSA, peptichemio, Bruceantin and Methyl-GAG. Also recent result of leukocyte interferon for breast cancer was obtained in M.D. Anderson Hospital. This information will be very useful for us to compare with the clinical study of fibroblast interferon in Japan.

Adriamycin, one of very potent drugs for advanced breast cancer, has troublesome cardiac toxicity. We are not using this drug so much extensively as in the United States, but we always concern about this side effect, especially on patients with irradiation to left chest wall. Technic to perform transjugular endomyocardial biopsy was shown in M.D. Anderson Hospital. We would like to introduce this method to our Hospital.

I could see hormone receptor assay in each laboratory. And I participated in two lectures on this matter during my trip: by

Dr. Joseph C. Allegra of NCI, and Dr. Ian Holdaway of Auckland Hospital in New Zealand. Dr. M. A. Friedman of UCSF showed me interesting data on other malignancies such as male breast cancer, renal cell cancer and malignant melanoma.

Annual Clinical Conference of M.D. Anderson Hospital was held during my stay, with the title of "Status of Curability of Childhood Cancer." It is encouraging for us to hear the word "cure", even in the other field.

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IV. INTERDISCIPLINARY PROGRAM AND COORDINATION AREA

IV. INTERDISCIPLINARY PROGRAM AND COORDINATION AREA

Program Coordinators: Dr. Robert W. Miller, U.S.A.
Dr. Haruo Sugano, Japan

1. ADMINISTRATIVE REPORT

Activities in this area during the past year focused on analysis of radiation related breast cancer, especially in the atomic-bomb survivors of Hiroshima and Nagasaki.

A. Seminars

1) A planning meeting for a "US-Japan Cooperative Pathology Study of Radiation Related Breast Cancer" was held at the Department of Pathology, Vanderbilt University, Nashville, Tenn., U.S.A. on July 16 to 20, 1979. The meeting was organized by Dr. Donald E. Henson, National Cancer Institute (NCI) and Dr. Shoji Tokuoka, Department of Pathology, Hiroshima University. (Also see p. 83)

2) A pathological review meeting and a summation meeting on "US-Japan Cooperative Pathology Study of Radiation Related Breast Cancer" was held at Radiation Effect Research Foundation (RERF, formerly ABCC) at Nagasaki and at Hiroshima on November 26 to December 4, 1979. The meeting was organized by Dr. Shoji Tokuoka, Hiroshima University and Dr. Donald E. Henson, NCI. Both Coordinators, Dr. Robert W. Miller and Dr. Haruo Sugano participated in the summation meeting. (Also see p. 85)

The purpose of this study is to determine if there are differences between breast cancer arising spontaneously in Japanese and American women and breast cancer developing in women exposed to radiation especially from the atomic bomb; and to determine, if data permit, the approximate minimal level of radiation required to induce breast cancer.

Results obtained:

At the planning meeting, the following was concluded.

(a) Breast cancer cases subject to be investigated are as many as 331. All of these have been registered in the Life Span Study Sample at RERF and are available for histological study. All exposed cases, composing approximately half of all cases, are expected to have estimated available of their radiation doses at the time of atomic bomb exposure (ATB).

(b) As a "pilot study", the breast tissue of autopsied nonbreast cancer cases, as many as 50, known to be irradiated with doses of 100+ rad ATB are to be investigated to detect potential premalignant histological lesions and/or chronic radiation effects on the normal tissues.

(c) As to the histological classification of breast cancer, one classification was adopted for this study, based on those proposed by WHO and the Japan Mammary Cancer Society.

(d) Data obtained through the histological work are to be analyzed by

bi-national representatives to complete the final report.

Following the planning meeting, a histological workshop on the basis of newly adopted histological standards of breast cancer as described above was at the same location by all participants.

The pathological review meeting was held at Nagasaki and Hiroshima. The collected cases to be investigated were as follows:

(a) Breast cancer in atomic bomb survivors 150 cases
(b) Breast cancer in non-exposed controls 150 cases
(c) Breast lesions in autopsied non-breast cancer patients, whose exposures were known to be 100+ rad 50 cases
(d) US radiation-related breast cancer, if any

The following was concluded at a summation meeting held in Hiroshima:

(a) The group confirmed that the number of breast cancer cases of atomic-bomb survivors is 149 and of non-exposed age-matched control is 153, totalling 302.
(b) It also confirmed that these 302 cases include those previously collected by McGregor et al. in 1971 and by Tokunaga et al. in 1978, and consist of all breast cancers known to have developed during the period of 1950 through 1978 among exposed and non-exposed females registered in the Life Span Study Sample at RERF.
(c) All participants agreed that subsequent analytical study of data accumulated through the histological study on these 302 cases is expected to be made by members of the bi-national participants, Dr. D. E. Henson and Dr. M. Tokunaga.
(d) Through the analytical work, the following should be elucidated: (1) the relationship between radiation dose and breast cancer development, and the minimal dose required for breast cancer development; (2) the relationship between breast cancer development and age ATB; (3) morphological characteristics of breast cancer in atomic-bomb survivors; (4) prognostic evaluation of breast cancer in atomic-bomb survivors; and (5) changes in the breast tissue attributable to ionizing radiation - as revealed by the "Pilot Study".

As to potential radiation-related breast cancer cases in the United States, it was reported by one of the US participants at the summation meeting that histological materials were not readily available from breast cancer among people who were treated with either repeated fluoroscopies of the chest or with x-ray irradiation for acute post-partum mastitis.

Preliminary Conclusions:

All cases were classified according to a combined WHO-Japan Mammary Cancer Society classification. The combined classification scheme was adopted so that results could be compared with international studies using the WHO format and with other studies conducted in Japan.

Based on a preliminary analysis, no significant difference was found in the distribution of histological types between the irradiated and non-irradiated groups. In fact, the distribution did not differ from the expected distribution of breast cancer in Japan as determined by other pathologists. Fundamentally, the distribution was not changed by considering the age ATB, age of diagnosis, interval from age ATB to diagnosis, and amount of irradiation. The peak age of diagnosis was the same in both groups. On the basis of this study, it was concluded that

radiogenic breast cancer does not differ histologically from spontaneously occurring breast cancer in Japanese women, and no histologic features were found that distinguish radiogenic from spontaneous breast cancer. It should be emphasized, however, that further data analysis is being made.

The pilot study revealed no residual atypical or epithelial proliferative lesions in either lobules or ducts. However, there was fibroelastotic degeneration of the stroma and atrophy of adipose tissue, changes that are associated with irradiation, but also found in other conditions, such as severe malnutrition.

B. Exchange of Scientists

The name of each visiting scientist is followed by his address, the dates of his visit, the names and addresses of all host scientists, and a brief description of techniques studies.

1) Dr. Jacob Furth, Columbia University Presbyterian Medical Center
Division of Health Sciences (Also see p. 87)

Dates: May 21-28, 1979
Host: Dr. Kenjiro Yokoro, Professor of Pathology
Hiroshima University, Hiroshima

2) Dr. Robert Yonemoto, Department of General and Oncologic Surgery
City of Hope National Medical Center, Duarte
California (Also see p. 88)

Dates: May 31 - July 7, 1979
Hosts: Dr. Seigo Fukuma, Chiba Cancer Center, Chiba 280
Dr. Haruo Sugano, Cancer Institute, Tokyo 170
Dr. Keijiro Kuno, Surgical Department, Cancer Institute Hospital, Tokyo 170
Dr. Masaru Izuo, Surgical Department, Gunma University Hospital, Maebashi 371
Dr. Yuichi Yamamura, Department of Internal Medicine, Osaka University Hospital, Osaka 553
Dr. Keishi Matsumoto, Institute for Cancer Research, Osaka University, Osaka 553
Dr. Hideki Koyama, Department of Surgery, The Center for Adult Diseases, Osaka 537
Dr. Takao Hattori, Department of Surgery, Hiroshima University Hospital, Hiroshima 734
Dr. Hiroshi Kobayashi, Cancer Institute, Hokkaido University Sapporo 060
Dr. Susumu Kishimoto, Department of Internal Medicine, Kumamoto University Hospital, Kumamoto 860
Dr. Takeshi Hirayama, Epidemiology Division, National Cancer Center Research Institute, Tokyo 104
Dr. Toshio Wagai, Medical Ultrasonics Research Center Juntendo University Hospital, Tokyo 113
Dr. Akio Matsuzawa, The Institute of Medical Science, The University of Tokyo, Tokyo 108

Dr. Yonemoto visited various laboratories that were working in the field of breast cancer and immunology, since his major interest was in the field of immunology of breast cancer. He obtained and exchanged knowledge on the following subjects from the Japanese scientists.

(1) Unique features of breast cancer in Japanese women, (2) immunotherapy, BCG cell wall skeleton, (3) newer diagnostic tools, and (4) animal models relevant to human breast cancer.

3) Dr. Donald E. Henson (Also see p. 89)
4) Dr. William Hartman (Also see p. 89)
5) Dr. Robert V. P. Hutter (Also see p. 89)
6) Dr. Masayoshi Tokunaga, Department of Pathology, Kagoshima University Medical School, Kagoshima 890, Japan (Also see p. 91)

Dates: January 15 - May 4, 1980

Hosts: Dr. Donald E. Henson, Laboratory of Pathology, National Cancer Institute, NIH, Bethesda, Md. 20205, U.S.A.

Dr. William H. Hartmann, Department of Pathology, Vanderbilt University, Nashville, Tenn. 37232 U.S.A.

Dr. Robert V. P. Hutter, Department of Pathology, St. Barnabas Medical Center, New Jersey 07039, U.S.A.

Dr. Tokunaga has been working with Dr. Donald E. Henson on a collaborative study of radiation related breast cancer at the NCI, NIH, Bethesda, Md. In addition, he has made a short visit to Dr. Hartmann's laboratory, and Dr. Hutter's laboratory for reviewing American breast cancer cases, including preoperatively irradiated cancer cases.

C. Exchange of Materials

A program for review of histopathological material on breast cancer in atomic bomb survivors has been developed by both Japanese and American groups. Dr. Tokunaga carrying histopathological slides visited Dr. Henson, NCI to make a collaborative study and to prepare a final report.

2. FUTURE ACTIVITIES IN RADIATION RELATED BREAST CANCER STUDY

1) Dr. Henson, NCI and Dr. Tokunaga, Kagoshima University have been preparing a joint report of this collaborative study of radiation related breast cancer at Pathology Laboratory, NCI, NIH.
2) All participants agreed to analyse possible changes in the breast tissue attributable to atomic-bomb irradiation. Dr. Toshio Fujikura, Head, Department of Pathology, RERF will provide a sufficient number of pathological specimens for this study under the cooperation of the NCI and RERF with close liaison to the US-Japan Cooperative Cancer Research Program.
3) American and Japanese groups agreed to examine histological changes of the breast tissue in preoperatively irradiated breast cancer cases. This study would reveal acute radiation damage of the breast tissue around cancerous nodules. Dr. Robert V. P. Hutter, New Jersey and Dr. Tokunaga reviewed pathological slides of such cases at St. Barnabas Hospital, New Jersey and Dr. Haruo Sugano and Dr. Goi Sakamoto will review cases at Cancer Institute, Tokyo. They will discuss abnormalities observed in different materials.

3. SEMINAR AGENDA AND PARTICIPANTS

1) A Planning Meeting for "US-Japan Cooperative Pathology Study of Radiation Related Breast Cancer"
Nashville, Tennessee, July 16-20, 1979

AGENDA

I. Seminar July 16-18, 1979	
1. Review of Previous Study on Breast Cancer Related to Radiation in both Japan and United States	Dr. S. Tokuoka Dr. D. E. Henson
2. Review of Previous Study on Breast Cancer in Atomic Bomb Survivors	Dr. M. Tokunaga
3. Plan of Present Study	
a. Case Material to be Included	Dr. D. E. Henson Dr. M. Tokunaga
b. Collection of Material	Dr. M. Asano Dr. T. Yamamoto
c. Classification of Breast Cancer	
1) New WHO Classification	Dr. W. H. Hartmann
2) Classification of Japan Mammary Cancer Society (JMCS)	Dr. G. Sakamoto
3) Classification to be Applied	Dr. R. V. P. Hutter
d. Protocol Design	Dr. D. E. Henson Dr. M. Tokunaga
e. Format and Time of Present Study	Dr. D. E. Henson
f. Analysis of Data and Final Report	Dr. S. Tokuoka
4. General Discussion	
5. Conclusion	

II. Workshop of Histological Classification
July 19-20, 1979

Each of the bi-national participants worked on histological tissue slides of 20 breast cancer cases that were prepared by the U.S. side, to classify each tumor. Following the microscopic work, all cases were reviewed and discussed by all until they came to agree on one conclusive classification on each case.

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2) Pathological Review Meeting on Radiation Related Breast Cancer
Nagasaki and Hiroshima, November 26 - December 4, 1979

AGENDA

Pathological Review at Radiation Effect Research Foundation (RERF) at Nagasaki November 26 - November 28, 1979

Pathological Review at RERF at Hiroshima November 29 - December 2, 1979

Summation meeting at RERF in Hiroshima December 3 - December 4, 1979

Session 1	Histological diagnosis of 302 cases of breast cancer in exposed and non-exposed females	Dr. S. Tokuoka Dr. D. E. Henson Dr. M. Tokunaga
Session 2	Histological classification adopted by this study group	Dr. W. H. Hartmann Dr. Goi Sakamoto
Session 3	Publication of results	Dr. S. Tokuoka Dr. D. E. Henson
Session 4	The findings and significance of histological changes of the breast tissue in "Pilot Study"	Dr. R. V. P. Hutter Dr. M. Asano Dr. T. Yamamoto
Session 5	Radiation related breast cancer cases in the U.S.A.	Dr. D. E. Henson

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4. SUMMARY REPORTS OF EXCHANGE SCIENTISTS

1) JACOB FURTH, Columbia University Presbyterian Medical Center
Division of Health Sciences

Host Institution: Dr. Kenjiro Yokoro, Professor, Pathology
Hiroshima University

Dates of Visit: Hiroshima Univ. May 21-24, Nagoya Univ. May 25-26
Osaka Univ. May 27-28, 1979

Summary of Activities:

Participation at meetings of the International Association on Late Effects of Ionizing Radiation (IALE) and Cancer Research Programs. I discussed Experimental radiation carcinogenesis, Implication of virus in leukemogenesis, Mammary carcinogenesis, Differences between the different types of radiations. As I pioneered in these areas, I could participate in the respective seminars. I also amplified the presently prevailing concepts on related topics, on which I worked during the past few years. These include: induction of functional transplantable pituitary tumors of all pituitary cell types; their hormonal interrelationship; stages of carcinogenes from dependent to autonomous; mutagenesis vs. carcinogenesis; carcinogenesis without carcinogens (by unrepaired replication error of DNA). Discussed the mechanism of carcinogenesis by estrogens; induction of pituitary tumors by birth control pills and their conceivable prevention.

Additional Information

These International Symposia in Hiroshima on late effects on ionizing radiation and neoplasia were organized and excellently managed by Dr. K. Yokoro. Dr. A. Ito, his associate (also my former trainee and co-worker in N.Y.C.) met me in Tokyo on arrival and remained my guide and translator until I departed from Tokyo to Nagoya.

The visits to Nagoya and Osaka were not in the original plan. Dr. A. Kunii, Professor of Experimental Pathology at the university of Nagoya, having learned of my projected trip to Hiroshima, invited me to delay my return to the USA by stopping at Nagoya. He organized a symposium for *May 25* on "Cancer as viewed by Experimental Pathologists". The chairman of the conference was Dr. R. Akazaki (Honorable Director of the Aichi Cancer Institute). Here, a historical revue was given (in Japanese) by the chairman of the Department of Pathology, followed by discussions (translated for me by Dr. Kunii).

On the session, Dr. Kunii asked me to lecture on "Recollections of my life in Cancer Research." This session was introduced and chaired by Dr. Hibino (Honorable President of the Nagoya National Hospital and Professor at Nagoya University).

May 26. Dr. Kunii took me to see Nagoya's Scientific Institutions and brought me together with medico-biologic scientists.

In Osaka, *May 27* similar arrangements were made by Dr. Ueda. His invitation followed that of Kunii (The Universities in Nagoya and Osaka are modern, next in size and scientific standing to that of Tokyo).

My discussions at all seminars in Japan were *ad hoc*, since I was not preinformed about the subject of their presentation except that on ionizing radiation. Altogether, my trip to Japan was a joyous occasion which cemented supernational understanding and friendship both, scientific and cultural.

2) ROBERT H. YONEMOTO, M.D., City of Hope National Medical Center
1500 East Duarte Road, Duarte, Calif. 91010

Host Institution: Prof. Haruo Sugano, Cancer Institute
Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan

Dates of Visit: May 31 - July 7, 1979

Summary of Activities:

The object was to secure first hand information regarding the present status of breast cancer in Japan and how it relates to the situation in U.S. Ten institutions were visited and approximately twenty some sessions were held to exchange current status of research as well as clinical progress by exchanging information. In addition to these individual small sessions, formal lectures were given by me on the topic of "Present Status of Breast Cancer in U.S.," "Immune Monitoring of Breast Cancer Patients," "Application of Transfer Factor as Immuno-therapeutic Agent in Breast Cancer," "A New Microslide Leukocyte Migration Inhibition Assay to Monitor Cell Mediation Immunity in Breast Cancer Patients."

The information I secured was invaluable from a standpoint of getting insight into the changing epidemiological picture of breast cancer in Japan which directly leads one to the understanding of causitive agents in breast cancer.

Publication resulting from this visit is "Breast Cancer in Japan and U.S.A." submitted to Archives of Surgery in January 1980. This same paper was also presented to the Southern California Chapter of the American College of Surgeons.

Abstract of "Breast Cancer in Japan and U.S.A."

Cancer of the breast represents the most common cancer (27% of all malignancies) among U.S. women, whereas in Japan it ranks third behind stomach and uterus in its frequency. In spite of the relative low incidence of breast cancer in Japan, a sharp increase in the frequency has been noted since 1966, which is decidedly related to change in dietary patterns in the Japanese women. An increase in over 250% of fat dietary intake has been noted during the past 15 years, mostly in the form of pork. Cancer is detected at an earlier stage in Japan as compared with the U.S., and, consequently, the end result is significantly better. But the improved results could not be totally explained on the basis of early detection, since stage for stage the Japanese series appears to be consistently better than the U.S. series by 10% in their 10 year survival rates. The effect of Atomic bomb radiation prevails even to this date. Women 10-30 years of age at time of A-bomb exposure show a continuous increase in the cumulative risk of breast cancer.

3)~5) BREAST CANCER PATHOLOGY STUDY GROUP

Members of the Study Group:

Dr. Donald E. Henson, Laboratory of Pathology, DCBD, NCI, National Cancer Institute, Bethesda, Md.

Dr. William Hartmann, Department of Pathology Vanderbilt University Nashville, Tenn.

Dr. Robert V.P. Hutter, St. Barnabas Medical Center, Livingston, NJ.

Sponsor: Dr. Haruo Sugano

Hosting Institute: Radiation Effects Research Foundation (RERF) Hiroshima and Nagasaki, Japan

Dates of Visit: November 23 to December 5, 1979

Summary of Activities:

"Report of Visit to Nagasaki and Hiroshima, November 24 thru December 5, to Review Histologic Material on Breast Cancer Patients Exposed to Atomic Irradiation"
Reported by Dr. Donald E. Henson, Laboratory of Pathology, DCBD, NCI

Left U.S. on Saturday, November 24, along with Drs. Hutter and arrived at Nagasaki on Monday, November 27 at 2:00 p.m. after an overnight in Tokyo. We were met at the airport by Dr. Asano, Pathologist at RERF in Nagasaki, and Dr. Tokuoka, Pathologist from Hiroshima University, and taken to the RERF building to organize our work. We spent the entire next day, Tuesday, November 28, reviewing case material from women exposed to atomic irradiation in Nagasaki. The plan of the study was to review the cases blind; that is, the three pathologists did not know in advance which case represented a control (non-exposed), or irradiated patient. In addition, the diagnoses were recorded independently so that one pathologist did not know the diagnoses of the other two. Seventy cases were reviewed in Nagasaki.

The following morning we traveled by train to Hiroshima and started our work on the afternoon of arrival. Our study which included 246 cases followed the same format used in Nagasaki. In Hiroshima, Wednesday, Thursday and Friday were required for the review. We were assisted by Dr. Tokunaga who helped with the clerical work and organization. On Friday afternoon, the U.S. pathologists reviewed the case material as a group in order to resolve any disagreements in diagnosis.

On Sunday, December 2, the five Japanese pathologists who had reviewed the cases in November prior to the arrival of the U.S. pathologists, assembled at RERF in Hiroshima. Included in the group were Dr. Yamamoto from RERF and Dr. Sakamoto from Tokyo, in addition to Dr. Asano, Dr. Tokuoka and Dr. Tokunaga.

On Monday, December 3, pathologists from both countries met

together in order to review the diagnoses and resolve any differences in diagnosis and classification that might exist. There was surprisingly little disagreement; only two cases were not resolved. In both cases, however, there was complete agreement that the diagnosis was cancer. The disagreement involved the particular histologic type. We attributed our general success to the fact that a preliminary meeting was held by the participating pathologists in Nashville, Tennessee in July, which afforded us the opportunity to become familiar with the classification scheme and diagnostic criteria used by the different pathologists. The classification scheme that we adopted was a combination of the World Health Organization's histologic classification of breast cancer modified to include the Japanese classification. By including the WHO classification, studies conducted in other parts of the world could be readily compared with our studies in Japan.

On Tuesday, December 4, the results of our work were presented in preliminary form to the staff of RERF including Dr. Sugano, Director of the Cancer Institute in Japan, who attended. Of 70 cases reviewed in Nagasaki, 63 were considered to be definitely cancer. In 6 cases, organs containing metastases were available but sections from the primary breast lesion could not be located. In these cases, a diagnosis of breast cancer was considered presumptive based on the appearance of the metastatic tumor. Of these 63 cases, 42 were from irradiated patients and 21 controls. Of 246 cases reviewed at Hiroshima, 240 were definitely considered to be cancer. This figure included 107 exposed and 133 non-exposed patients. It should be noted that a case of primary lymphoma of the breast was discovered in the control group. Again, 6 cases were not diagnosed as cancer, but considered presumptive since sections from the primary breast lesion were not available.

In addition to the women with breast cancer, a pilot study was conducted which consisted of reviewing breast material from 56 women who were exposed to 100 rads or more, but who did not have a diagnosis of breast cancer. The purpose of the review was to search for precancerous lesions that did not progress to neoplasia or persistent atypical hyperplasia. Our results showed no hyperplasia or atypical lesions, but atrophy, some degeneration of fat, and a peculiar fibroelastotic degeneration of the stroma, a change that is known to be associated with irradiation. These findings were thought by the pathologists to warrant further studies on the potential effects of irradiation on breast tissue.

There was general agreement that the bi-national study was a successful one. A list of patients indicated by master file numbers along with the final diagnoses will be submitted to RERF. In addition, results of the study will be published in a scientific journal.

During the general summation on December 4, and during informal discussions that followed, there was a consensus that the work should be pursued. It was decided to expand the pilot study to include appropriate controls and a larger number of patients because of the unexpected finding of fibrosis and severe atrophy. There was some discussion but no consensus regarding the extent these lesions occur in the normal breast of Japanese women. Furthermore, Dr. Sugano was enthusiastic about the possibility of RERF sponsoring a symposium on the acute, chronic and long-term effects of radiation on breast tissue.

The symposium seems timely in view of the increase in our knowledge concerning the affects of irradiation on breast tissue. Finally, it should be noted that Dr. Tokunaga, one of the participating pathologists, will work in the U.S. as a Visiting Scientist for three months beginning in February. He will review, as one task, breast material removed from women who had a diagnosis of cancer and who received large therapeutic doses of irradiation prior to mastectomy. In addition, a number of cases have been collected concerning women who had a diagnosis of chronic mastitis and who were treated by irradiation and subsequently developed cancer. It is hoped that Dr. Tokunaga will be able to review these cases while in the U.S.

On behalf of the participating U.S. pathologists, I would like to thank the staff at RERF both in Hiroshima and in Nagasaki as well as the Japan Society for the Promotion of Science and the NCI for approving and supporting this work. We hope to be able to obtain additional support for future studies related to radiation and the breast.

6) MASAYOSHI TOKUNAGA, M.D., IInd Department of Pathology, Faculty of Medicine, Kagoshima University

Host Institution: Dr. Donald E. Henson, Laboratory of Pathology, National Cancer Institute, NIH, Bethesda, Md.

Dates of Visit: January 15 to May 4, 1980

Summary of Activities:

A series of epidemiological studies have indicated a significantly greater incidence in the occurrence of breast cancer in Japanese women exposed to atomic irradiation than comparable women not exposed. The purpose of this study is to compare the histological differences of breast cancer cases exposed and non-exposed. There were 303 breast cancer cases, 149 irradiated and 155 non-irradiated, among the extended LSS sample of RERF. Five Japanese and three American pathologists reviewed the slides.

The results of the study showed no significant difference in the distribution of the histological type between exposed and non-exposed groups or between two cities, Nagasaki and Hiroshima. There is no significant difference in either group in the distribution of histological types according to age of diagnosis or from the time of age at bombing to diagnosis. The age distribution of breast cancer cases at the time of bombing for the exposed and non-exposed groups show significant different among these two groups.

APPENDICES

BEST DOCUMENT AVAILABLE

PLAN FOR SECOND FIVE-YEAR PROGRAM

Purpose

The U.S.-Japan Cooperative Cancer Research Program was initiated in 1974 between the National Cancer Institute (NCI) and the Japan Society for the Promotion of Science (JSPS), with a view to eventually conquering cancer, a common enemy of mankind. The United States and Japan respectively developed cancer research under different academic and cultural systems. Furthermore, cancers in the two countries show different characteristics from the viewpoint of geographic pathology. Special significance was mutually recognized of planned cooperation between the scientists of the two countries with such different backgrounds. The first five-year cooperative program comprised scientific seminars, exchange of scientists, and exchange of research materials and information, and covered eleven areas of cancer research.

The achievements during the first five-year period are described in detail in the First Progress Report (1974-75), the Second Progress Report (1976-77), and the Third Progress Report (1978). Notable progress was witnessed in the eleven areas of cancer research. Among the important achievements of the cooperative program are comparison of cancer patterns of the two countries, development and application of carcinogen and mutagen assay methods, introduction of new technology in cytology automation, high LET radiation, comparative study on new antitumor drugs, and the establishment of a fundamental basis of immunotherapy. The Program made it possible for a large number of cancer researchers of the two countries to be acquainted with each other through research and discussion. Such a personal contact is also a great achievement of the Program, which is intangible but highly stimulating for the progress of cancer research in the respective countries.

With these achievements and experience during the first five-year period, the Second Five-Year Cooperative Research Program will be started in 1979 to further the common purpose of diminishing disability and death from cancer.

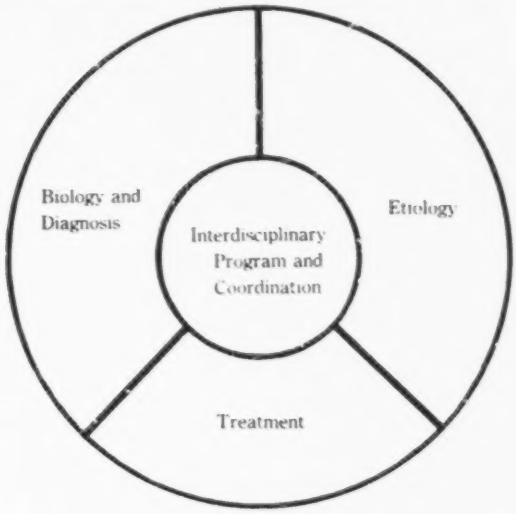
The main objectives are as follows:

1. To identify environmental and intrinsic carcinogenic factors and mechanisms through laboratory and epidemiological research in order to further the understanding of causes of cancer and means of its prevention.
2. To clarify the nature of cancer cells from the stand-point of cellular and molecular biology; to explore further the nature of fundamental immunologic processes that may determine host responses to cancer; and to develop new methods for the early diagnosis of cancer.
3. To develop new anticancer drugs, new developments in radiation oncology, new immunotherapeutic approaches, and combined modality studies most appropriate to specific disease sites. Collaborative trials will be undertaken to compare results in

both countries and to maximize the rapid accumulation of meaningful data. Disease sites to be emphasized include gastric cancer, lung cancer, breast cancer, and bladder cancer.

Areas for Cooperation

The following four major areas for cooperation will be newly established in place of the previous eleven areas, so as to give greater flexibility in carrying out cooperative research:



The Interdisciplinary Program and Coordination Area serves the functions of general coordination of the three program areas, consideration of new programs of scientific merit, and facilitation of interdisciplinary program areas of high priority and other organ sites.

The restructuring of the areas for cooperation is required by the present social needs of the two countries and recent cancer research progress in the world, as well as from the experience of the first five-year program.

Each area will have two coordinators, one appointed by each country. A number of areas of special interest may be identified for each area to indicate priority in the implementation of cooperative activities. These areas of special interest may change during the five years, depending on the scientific opportunity and new knowledge. Coordinators may appoint principal advisors to assist them in developing the areas of special interest as they evolve.

The areas of special interest are as follows:

I. *Etiology*
   - Epidemiology
   - Chemical and Radiation Carcinogenesis
   - Viral Carcinogenesis
   - Genetics

II. *Biology and Diagnosis*
   - Cellular and Molecular Biology
   - Immunology
   - Diagnosis

III. *Treatment*
   - Chemotherapy
   - Radiation Oncology
   - Immunotherapy
   - Clinical Trials

IV. *Interdisciplinary Program and Coordination*
   - Overall coordination of above three program areas
   - Consideration of new programs or special areas of interest
   - Sponsoring of interdisciplinary sessions
   - Organ sites

New Machinery for Implementation

1. The Joint Steering Committee Meeting as a policymaking group will meet at least once every year.
2. The Joint Steering Committee Meeting will discuss the following matters:
   - Policy matters concerning the U.S.-Japan Cooperative Cancer Research Program
   - Overall plan for the Second Five-Year Program
   - Annual program including scientific seminars, exchange of scientists, and exchange of materials and information
   - Matters concerning the coordination among the program areas for cooperation
   - Matters concerning inter/multidisciplinary programs
   - Evaluation and report of activities
   - Any other matters which need agreement between the NCI and the JSPS.

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3. Participants of the Joint Steering Committee Meeting will be the representatives and executive secretaries of NCI and JSPS and the program coordinators of the four areas. If deemed necessary, special guests may be invited to participate in the meetings as ad hoc members.

4. The agreements reached at a Joint Steering Committee Meeting will be effective as approved by both NCI and JSPS.

5. The NCI and the JSPS will maintain close contact by occasional meetings or correspondence to prepare for the Joint Steering Committee Meetings and to consult with each other in regard to the implementation of the cooperative program.

Types of Activity and Financial Responsibilities

Activities that will be supported by the NCI and the JSPS under this cooperative program are (1) scientific seminars, (2) exchange of scientists, and (3) exchange of materials and information. Each type of activity will be carried out as follows based upon the priority and availability of the funds:

1. **Scientific Seminars.** The NCI and the JSPS will support selected scientific seminars and workshops in fields that are rapidly developing or in need of development, on the basis of the proposals submitted by the coordinators of each area or by the principal advisors through the coordinators concerned, within the framework of the annual program approved by the Joint Steering Committee Meeting. The NCI and the JSPS will share the cost of these seminars including travel, living allowance, and other expenses of their own participants.

2. **Exchange of Scientists.** The NCI and the JSPS will support the exchange of a limited number of American and Japanese scientists either for a short-term period or a long-term period, on the basis of the proposals submitted in a similar way as prescribed in the preceding paragraph. Such exchange is not intended for training but for promoting cooperation. The NCI and the JSPS will pay the travel and living allowance of their own participants.

3. **Exchange of Materials and Information.** The NCI and the JSPS may promote and develop the exchange of materials and information between the scientists and clinical investigators in the two countries and share the cost of such exchanges.

4. **Direct Collaboration.** As an outgrowth of seminars and the exchange of scientists, direct collaborative activities may develop and these activities will be facilitated.

5. **Others.** The Program will not fund research projects or activities other than those listed above.

Procedure for Program Preparation

1. Within the framework of the overall plan of the Second Five-Year Program, the coordinators of each area will prepare a proposed annual program plan of their area, in consultation with the principal advisors, if necessary. Such a program plan should indicate priority subject matters of that program area as well as the proposed number of projects for each type of activity.

2. These proposed program plans will be submitted to the Joint Steering Committee through the respective implementing agencies. The Joint Steering Committee will consider these program plans as submitted and make recommendations.

3. Within the framework of the annual program plans considered by the Joint Steering Committee Meeting, the coordinators will prepare, in cooperation with principal advisors, specific proposals for each type of activity and submit them to the respective implementing agencies.

4. The implementing agencies will consult with each other and, if agreed, they will notify the coordinators concerned of their approval of the proposals, which then will be implemented.

5. For the first year of the Second Five-Year Program, a special procedure will be utilized by the NCI and the JSPS to facilitate the implementation of the cooperative program.

Minutes of the First Meeting of the Joint Steering Committee
San Francisco, California, U.S.A. May 24-25, 1979

The meeting was called to order at 9:00 A.M. by Dr. Robert W. Miller, Director, Office of International Affairs, National Cancer Institute, and Co-chairman of the Joint Steering Committee.

The attendees for the Japanese Committee were Dr. Haruo Sugano, Co-chairman of the Joint Steering Committee, Drs. Yuichi Yamamura, Yoshio Sakurai, Takashi Sugimura, Mr. Kichimasa Soda, representing the JSPS, and Ms. Toshiko Takeuchi, JSPS. The U.S. was represented by Drs. Robert W. Miller, Stephen K. Carter, I. Bernard Weinstein, Robert R. Omata and Mrs. JoAnne Day. Unfortunately, Dr. William Terry was unable to attend due to his attendance at the meeting of the National Cancer Advisory Board in Bethesda, Maryland.

Dr. Miller welcomed the Japanese members and mentioned that it has been a great change for him from substituting for Dr. Newell at the June 1978 meeting to becoming Co-chairman of the Joint Steering Committee. He expressed his hopes that this meeting would be as imaginative as possible in discussing the plans for the future and that different ideas could be fused to create a very dynamic program. He encouraged everyone to express opinions fully.

Although Dr. Guy R. Newell has resigned as Co-chairman, due to additional and pressing responsibilities, he strongly believed that the US-Japan Co-operative Cancer Research Program was one of the best bilateral programs sponsored by the NCI. Dr. Newell extended his best wishes to the Joint Steering Committee.

Mr. Soda, representing the Japan Society for the Promotion of Science, expressed the appreciation of the Japanese members and the JSPS for the arrangement of this meeting in San Francisco by the OIA Staff. He congratulated Dr. Miller on his appointment as Director, OIA. He also stated that Dr. Newell was also responsible for the success of the first five years of the Program through his leadership and support.

He then stated that this meeting was the first formal meeting of the Joint Steering Committee to develop plans and implement the Program for the second five years of the Program. He stated that JSPS is in full agreement on the new program structure in order to implement an efficient and flexible program. Thus far, the Program has been a great success and it has made a considerable impact on cancer research in both countries. He reported that during the first five years of the Program, 46 seminars, meetings and workshops were sponsored with over 1,000 total participants, and that 80 Japanese and 55 American scientists were selected as Exchange Scientists to engage in collaborative research activities. In addition, several research collaborations were instigated as corollary activities to the US-Japan Program and were not officially supported by Program funds.

He reported that the JSPS budget has not been increased over last year's

funds, but he believed that quality and not quantity of activities was the measure of the progress of a successful cooperative program.

At the last meeting of the Committee in November 1978, the members congratulated Dr. Takashi Sugimura for being awarded the Imperial Medal for Culture by the Emperor of Japan. This time the Committee congratulated Dr. Miller for his new position as Director, Office of International Affairs, NCI, and also Dr. Omata for being awarded the PHS Meritorious Medal by the Surgeon General, Public Health Service.

Mr. Soda then thanked the NCI staff and Dr. Carter for making the meeting arrangements. He introduced Ms. Toshiko Takeuchi, who has succeeded Mrs. Yuko K. Furukawa on the US-Japan Program. She has spent several years in the U.S., most recently serving three years at the Japanese Embassy in Washington, D.C. He reported that Mrs. Furukawa just recently became the mother of a baby daughter. The Committee extended its collective congratulations and best wishes to Dr. and Mrs. Furukawa.

Dr. Omata announced that the U.S. side was inviting the Japanese members to an informal dinner at Fisherman's Wharf. Mr. Soda invited the U.S. side to a luncheon to be held in old Chinatown in San Francisco.

Dr. Sugano, Co-chairman of the Joint Steering Committee, expressed his pleasure in co-charing this meeting with Dr. Miller and announced that beginning April 1, the newly structured US-Japan Program was effective.

He stated that the Chemotherapy Meeting was just completed in San Francisco and simultaneously the High Energy Radiation Therapy Meeting was held in Kyoto, Japan, May 22-23, 1979, both sponsored under the Cancer Treatment Program Area.

He expressed his hopes and beliefs that the second five years would stimulate increased cooperation and bring about many fruitful results. He stated that there has been mutual agreement on the new structure and basic policies and principles of the Program. The main purpose of this meeting was the following:

1. Discuss and confirm basic plans and policies;
2. Discuss program plans for the future; and
3. Discuss the basic strategy for the next five years.

Mr. Soda presented the latest version of the Program plan of the US-Japan Cooperative Cancer Research Program. (See pp. 93-95) The committee unanimously accepted the Program Plan.

Drs. Sugimura and Weinstein were asked to present the plans for the Etiology Program Area. They first reported that Cancer Prevention has become a major issue, not only nationally, but on an international basis. Dr. Weinstein proposed that Prevention might be duly corsidered as a topic for the biennial Interdisciplinary Program topic for 1980. Dr. Miller reported that Prevention has become a very popular topic recently and that the subject could have a great impact on the direction of cancer research in the near future; namely, the relevance of low-dose radiation effects and other environmental factors.

Dr. Sugimura reported that Prevention has become a topic of considerable discussion in Japan. The Radiation Effects Research Foundation (RERF, formerly the ABCC) has been interested in the subject. He also stated that it may be possible to obtain a supplemental increase of funds for research on prevention. Dr. Miller feels that U.S. activities in Prevention may be able to motivate Japan to increase research support.

Drs. Sugimura and Weinstein then named the persons who will act as advisors for the Etiology Program Area.

I. Epidemiology:
Takeshi Hirayama, National Cancer Center Research Institute
Robert W. Miller, National Cancer Institute

II. Chemical and Radiation Carcinogenesis:
Shozo Takayama, Cancer Institute
Harry B. Gelboin, National Cancer Institute

III. Viral Carcinogenesis:
Hiroto Shimojo, Institute of Medical Science, University of Tokyo
Hidesaburo Hanafusa, Rockefeller University
Thomas Benjamin, Harvard University

IV. Genetics:
Susumu Nishimura, National Cancer Center Research Institute
Warren Nichols, Institute for Medical Research, Camden, New Jersey

Then Dr. Sugimura reported that plans are being made to sponsor the following meetings under the Etiology Program Area:

1. "Colo-rectal Cancer and Gastric Cancer - Its Epidemiology, Initiator and Promotor."
Organizers: T. Hirayama (National Cancer Center Research Institute, Tokyo)
S. Takayama (Cancer Institute, Tokyo)
J. H. Weisburger (American Health Foundation, NY)
W. R. Bruce (Canada)

Place: Hawaii (East-West Center, University of Hawaii)

Dates: March 3-5, 1980

Participants: 10-15 from each side

Possible Subjects or Topics:
Nitrosamines, migrant studies in Hawaii, nutrition studies (fats and fibers), high-risk families, chemoprevention, differences in incidence of gastric cancer and colon cancer.

The advantage of holding this meeting in Hawaii is to draw on the experts there, especially on the Japanese migrant population studies.

2. "DNA Polymerase"

Organizers: D. Korn (Stanford University)
K. Koike (Cancer Institute, Tokyo)

Place: Tokyo

Dates: March 1980

Dr. Weinstein reported that little is known about the biochemistry of DNA replication, especially in mammalian cells. This area of research is rather new and techniques are very different. The meeting will be very timely. Dr. Sugano stated that Dr. Koike has been in communication with Dr. Korn and that this should be a good meeting. Dr. Weinstein stated that this meeting will complement the earlier meeting on "RNA Repair and Misrepair" held in Kyoto in 1977.

3. "Biochemical Epidemiology"

Organizers: Allen Conney (Hoffman, LaRoche, New Jersey)
S. Nishimura (National Cancer Center Research Inst.)

Place: U. S.

Dates: Fall 1980 or Early 1981

Scientist Exchange for Etiology Program Area:

1. Epidemiology:

a. Hiroyuki Shimizu, Aichi Cancer Research Institute
Sponsors: R. W. Miller, NCI, and Brian Henderson,
University of Southern California - 3 months.

b. Takeshi Hirayama, National Cancer Center Research Institute
Sponsors: R. W. Miller, NCI, National Library of Medicine,
and Dr. A. Hollander

2. Chemical and Radiation Carcinogenesis:

a. Kazuo Umezawa, Tokyo University
Sponsor: I. B. Weinstein, Columbia Univ., Sept.-Oct. 1979

b. Norio Matsukura - National Cancer Center Research Institute
Sponsor: Harold Stewart, NCI, 3 weeks September 1979

c. Neil Spingarn, American Health Foundation
Sponsor: Matsushima and Sugimura, 3 months Oct.-Dec. 1979

3. Viral Carcinogenesis:

a. Masakazu Hatanaka, NCI
Sponsor: Professor T. Sugahara, Kyoto University
6 weeks Sept.-Oct. 1979

b. One to be nominated by Japan

Mr. Soda reported that the JSPS Budget for 1979-80 will provide funds to support 10 meetings and 28 man months for Exchange Scientists from Japan.

The question of publicizing the Scientist Exchange under this Program was mentioned. This subject was discussed, and it was generally felt that the Exchange of Scientists should not be publicized since there is a limited amount of funds, and the exchange of scientists in the future should be program related.

Dr. Sugimura reported that 10 gram samples of tryptophane and glutamic acid pyrolysates have been provided to the U.S. for research purposes. Dr. Takeo Kakunaga, NCI, will act as the U.S. resource person. Dr. Weinstein expressed his appreciation for the pyrolysates, since they are valuable resources for carcinogenesis research.

Professor Yuichi Yamamura was asked to report on the program plans for the Cancer Biology and Diagnostic Program Area, since Dr. Terry was unable to attend. Professor Yamamura stated that he would report for both Program Coordinators.

Cancer Biology and Diagnosis Program Area:

Program Coordinators: Professor Yuichi Yamamura, Osaka University
Dr. William Terry, NCI

Advisors:

I. Cellular and Molecular Biology:

Dr. Yoji Ikawa, Cancer Institute, Tokyo
Dr. Ira Pastan, NCI

II. Immunology:

Dr. Toshiyuki Hamaoka, Osaka University
Dr. Richard Hodes, NCI

III. Automated Cytology:

Dr. Yoshio Tenjin, Kyoundo Hospital, Tokyo
Dr. Myron Melamed, Memorial Sloan-Kettering Cancer Center, NY

Dr. Yamamura outlined the various research sub-areas which will be covered in the future under the Cancer Biology and Diagnosis Program Area.

I. Cellular and Molecular Biology

a. Alteration of cellular gene expression in transformation caused by known transforming sequence in oncoviruses.

b. Altered gene expression in neoplastic cells.

c. Cell to cell interaction in cancerous state.

d. Cancer phenotypes, especially those of cell membranes.

e. Interaction between cancer tissue and its surrounding tissues.

f. New experimental animal models.

The tentative subjects are interrelated and joint activities, including seminars and scientist exchange, will be related to these subjects.

II. Immunobiology

a. Antigenic nature of tumor cells.

b. Fundamental immunologic process in host response to tumor.

c. New approaches and preclinical trials in tumor immunotherapy.

III. Diagnosis

a. Automated cytology

b. Flow-system monitoring of chemotherapy and immunotherapy.

The above programmatic sub-areas have been tentatively projected for the next five years, however, the subjects may change depending on the discussions between the principal advisors for each of the sub-areas.

The program activities for 1979 have been generally agreed upon as follows:

1. Meeting on "Origin and Function of Specific Transforming RNA Sequences in Oncoviruses - Study on *src* and *leuk* Genes".

   Organizers: Dr. Ira Pastan (NCI)
   Dr. Peter Vogt (University of Southern California)
   Dr. Yoji Ikawa (Cancer Institute)
   Dr. Kumao Toyoshima (Institute of Microbial Diseases, Osaka University)

   Dates: November 12-14, 1979

   Place: Bethesda, Maryland

   Participants: 12 for U.S. and 8 for Japan

2. Seminar on "Mechanism of Host Tumor Immunity and the Theoretical Basis for Tumor Immunotherapy".

   Organizers: Dr. Richard Hodes (NCI)
   Dr. Toshiyuki Hamaoka (Institute for Cancer Research, Osaka University Medical School)

Dates: October 7-10, 1979

Place: Maui, Hawaii

Participants: Under negotiation

3. Seminar on "Automated Cytology"

Organizers: Dr. Myron Melamed (Memorial Sloan-Kettering Cancer Center, New York)
Dr. Yoshio Tenjin (Kyoundo Hospital, Tokyo, Japan)

Dates: October or November 1979

Place: Asilomar, California

Participants: Under negotiation

For the exchange of scientists, the scientists involved will be related to the areas of collaborations sponsored under the Program Area. For the immediate future Dr. Masuo Obinata, Cancer Institute, Tokyo, Japan, will be nominated for molecular biology to study with Dr. A. W. Neinhuis, National Heart, Lung and Blood Institute, NIH, for 2 months. Others are being considered in Immunology and Diagnosis Areas.

Dr. Yamamura and his research group are preparing samples of *Nocardia* cell wall skeleton antigen to be sent to NCI for Phase I and II studies in immunotherapy. Preliminary studies in Japan show that the antigen is quite effective in treating lung cancer.

The Cancer Biology and Diagnosis Program will have exciting new areas to be covered in the future. Dr. Yamamura stated that good programming will be needed to explore the new area. Dr. Miller feels that the Steering Committee may be helpful in assisting in bringing up new areas. Dr. Carter reported that clinical immunotherapy of lung cancer has raised new interest and should be considered for a meeting under Cancer Treatment.

The subject of automated cytology was discussed. It is possible that this subject may continue for the next five years, but it would depend on the advances to be made during the next year.

The subject of scientist exchange was discussed again. There are several other sources to support exchanges, namely the NIH Visiting Program, Fulbright-Hays Program, Fogarty International Research Exchange Program and the JSPS Fellowships for foreign and Japanese scientists.

The meeting was recessed for lunch at the Great Eastern Restaurant, hosted by the JSPS. The meeting was reconvened after lunch.

Drs. Sakurai and Carter were asked to present the program developed for Cancer Treatment Program Area. The Cancer Treatment Area will organize seminars and symposiums based on chemotherapy, radiation therapy and immunotherapy, and orient the methods of treatment of cancers of the

bladder, lung, breast and stomach. There are new opportunities to be explored in the treatment of other types of cancer not currently covered under the Program.

Dr. Sakurai reported that the Japanese working group has been selected as follows:

Program Coordinator: Dr. Yoshio Sakurai
Breast Cancer: Hiroki Koyama, Center for Adult Diseases, Osaka
Gastric Cancer: Makoto Ogawa, Cancer Institute
Lung Cancer: Shoji Hattori, Center for Adult Diseases, Osaka
Immunotherapy: Yuichi Yamamura
Radiation Oncology: Akira Tsuya

U.S. Program Coordinator: Dr. Stephen K. Carter
Preclinical Drug Development: John Douros, NCI
Abraham Goldin, NCI
Chemotherapy: Franco Muggia, NCI
Immunotherapy: Steven Rosenberg, NCI
Radiation Oncology: Glenn Sheline, University of California, San Francisco

During 1979 three meetings have been planned, of which two were just completed:

1. High LET Radiation Therapy Meeting.

   Organizers: Akira Tsuya and Glenn Sheline

   Place: Kyoto, Japan

   Dates: May 22-23, 1979

   Participants: 25 Japanese and 25 Americans

2. "New Drugs under Clinical Evaluation and Their Application in Treatment of Solid Tumors"

   Organizers: Stephen Carter and Yoshio Sakurai

   Place: San Francisco

   Dates: May 22-23, 1979

   Participants: 9 from Japan and 20 from the U.S.

3. "Background and Newest Modality in Lung Cancer Treatment in the United States and Japan"

   Organizers: Under discussion

   Place: Tokyo

Dates: November 1979 or early 1980

Participants: 8-10 from Japan, 5-10 from U.S. depending on site

This meeting will be a discussion on the multi-disciplinary approach to the treatment of lung cancer, in studying radiation therapy, chemotherapy and immunotherapy. There is new exciting data on the treatment of oat cells in lung cancer, which comprises 20% of the lung cancer cases. Also new data on the Nocardia cell wall skeleton vaccine show very interesting results.

At the last business meeting of the Cancer Treatment Program Area, tentative program plans were discussed. It was decided that the following meetings will be plann

1. Two-day symposium on the development of new analogues and drug studies.

   The new analogues of bleomycin and adriamycin such as Pep-bleomycin and aclynocinomycin as well as new analogues of nitrosoureas and fluoridated pyrimidine will be discussed.

2. Breast Cancer Treatment Meeting

   Organizers: Under discussion

   Place: San Antonio, Texas

   Dates: Fall 1980

   Topics: Adjuvant therapy, chemotherapy and hormone therapy, hormone receptor and local control of disease.

3. Bladder Cancer Treatment

   Organizers: Under consideration

   Place and date: Under consideration

   Topics: Use of cis-platinum, adriamycin and radiation therapy, other chemotherapeutic drugs, and bladder cancer treatment as related to other cancers.

Dr. Carter reported that, in addition to the formal cooperation under the Program, the Joint Study of Gastric Cancer Treatment between the Northern California Oncology Group and the Japanese Group has made remarkable progress. The cooperative studies have been excellent. The preliminary data treatment results have been comparable and the survival rates have also been comparable. Although the total numbers have been limited, the studies show promises of effective treatment, particularly with chemotherapy after surgery. This study shows that joint cooperative studies can be worked out on comparable basis when they have been well-planned in advance. It is possible that a future study on breast cancer treatment will be effected.

Dr. Sugimura brought up the problem of the criteria used for treatment and cure in Japan. Dr. Sakurai stated that it is very important that such studies should use similar clinical protocols and criteria for staging and treatment results. Dr. Carter stated that chemotherapy has reached a point for evaluation over other types of therapy. Future work will be focused on the role of drugs in multidisciplinary treatment. He also stated that the development of new drugs in Japan has reached a stage where the methods for treatment are changing. He feels that the free enterprise system in Japan has made it possible to create competition and innovation in the development of new drugs. The criteria to measure response to drug treatment is being changed with new treatment methods. There is an increased intensity of interaction among the clinical researchers to exchange ideas and views.

Dr. Sugano brought up the subject of chemoprevention. Dr. Carter reported that 13-cis retinoic acid; a Vitamin A analogue, is being tested in a bladder atypia study. There is some data on the effective reversal of the pre-cancerous process.

Dr. Carter stated that clinical study on gastric cancer has shown there is comparability of clinical results and this can be a model for other clinical studies. At present, the total numbers are not adequate. More data will be needed in the future to evaluate the results. Dr. Sakurai anticipated the development of more cooperation in chemotherapy studies in the future. Studies on side effects, as well as qualitative and quantitative results of drug therapy will be necessary in the future. Dr. Carter stated the biostatistical analyses in clinical studies are very important and that there is need for further advances in the use of biostatistics.

Dr. Sakurai believes that long-term scientist exchanges of young Japanese scientists may not be necessary in their Program Area but exchanges should be concentrated on specific subject areas and clinical trials. He feels that clinical trials should be continued since they will help remedy the short-fall in methodology in medical oncology in Japan. He would like to see more young Japanese specialists study the American procedure in treatment and data analysis of clinical trials. Both Drs. Carter and Miller agreed that even in the U.S. there is a lack of good clinical epidemiologists studying and analyzing clinical trials.

At present there is no formal certification of oncologists in Japan. Currently there are residency training programs in oncology at the National Cancer Center Hospital in Tokyo and at the Institute of Adult Diseases in Osaka.

Dr. Sugano stated that the Interdisciplinary Program Area has the responsibility to coordinate the whole US-Japan Cancer Program and to provide support for new or special areas of interest. In addition, meetings on multi-disciplinary aspects of organ site and the biennial large conferences will be sponsored by this Program Area. The advice of the Joint Steering Committee will be asked to formulate the programs for this area.

Dr. Miller stated that the Joint Steering Committee members should suggest

new areas of interest as well as make recommendations for special topics or subjects for the biennial conference. New advances in cancer research and special topics with emphasis on the US-Japan Cancer Program and interdisciplinary subjects should be stressed. The subject of nutrition and cancer was brought up. It was decided that there have been few new developments in the nutrition field and a meeting in the near future is not necessary. It was agreed that a conference on "Recent Advances and New Approaches to Cancer Research" be sponsored in Japan during the second week of June 1980, possibly in the Kansai area. The Joint Steering Committee will also be meeting either prior to and/or after the conference.

It was agreed that in the future annual summary reports will be prepared by the Program Area Coordinators and be published. A format for the reports should be devised for consistency of the format.

Mr. Soda reported that the JSPS has formed an Advisory Committee for the US-Japan Cooperative Cancer Research Program to provide overview and policy recommendations to the JSPS.

The meeting was adjourned at 5:00 PM and it was agreed that the Committee would meet at 9:00 AM on Friday, May 25th.

The NCI hosted a dinner for the Japanese members of the Joint Steering Committee at Fisherman's Wharf.

The meeting was called to order by the Chairmen: Dr. Sugano and Dr. Miller at 9:00 AM.

Early discussion was centered on time and place of next Joint Steering Committee Meeting.

It was agreed to hold the biennial conference in the Kansai area of Japan, either in Nara and Osaka. The first day would be devoted to the Joint Steering Committee Meeting and on the second and third days the scientific meeting will be held. It was generally agreed that 45 minutes be allocated for each presentation, with three per session i.e., 30 minutes per presentation and 15 minutes for discussion. Dr. Sugimura suggested that a short follow-up meeting of the Joint Steering Committee be held on the fourth day to discuss any new items of interest brought up by the scientific meeting. The Program Coordinators will agree on the subject to be discussed.

Dr. Weinstein suggested that a book of abstracts of the presentations be prepared for public distribution.

Dr. Miller brought up the subject of poor quality of slides and expressed hope that the slides could be prepared at one place (perhaps by NIH) to avoid poor quality of slides.

Dr. Weinstein mentioned that the American Association for Cancer Research (AACR) has guidelines for slides. He stressed the need for the cooperation of all speakers in the preparation of good slides.

Dr. Sugano and Mr. Soda discussed support from the Japanese side for the large scientific meeting. It was thought that the JSPS and the Japanese Cancer Association could provide support.

Dr. Miller suggested that a summary of the meeting be published. Dr. Weinstein suggested the possibility of also publishing a report of the meeting in *Cancer Research*, of which Dr. Peter McGee is the Editor.

Dr. Miller suggested that abstracts be provided to participants and interested individuals in advance of the meeting.

The question was raised if the meeting should be published in Japanese as well as English. Dr. Sugimura stated that it was unnecessary to publish in Japanese.

Mr. Soda stated that it might be appropriate to have some time for general discussions after the scientific session. The group felt that this discussion could be held after the large meeting at the continuation meeting of the Steering Committee.

The subject of cancer prevention was then brought up. Dr. Weinstein stated that current NCI plans reflect the trends and pressures from the public. Dr. Miller stated that Dr. Upton will create a new entity - Division of Cancer Prevention. The Division of Cancer Control will be eliminated and replaced by the Division of Cancer Resources, Centers and Community Programs. This will include cancer centers and organ site programs.

Dr. Weinstein stated that there is considerable pressure from Congress to emphasize Cancer Prevention.

Dr. Sugimura stated that concern about Prevention was world-wide. He felt that with the great emphasis on Prevention, perhaps more funds could be appropriated for the Program.

Dr. Weinstein brought up the recent problems with dumping of hazardous wastes, regulatory procedures, etc. He stated that this new area of prevention will deal with many entirely new problems and possible solutions, such as disposal of chemicals, behavior modification related to smoking, etc. Dr. Miller reiterated that what Dr. Weinstein was saying was that with the new field of Prevention becoming more visable and important, the Interdisciplinary Program Area will have to cover this area as well.

Dr. Yamamura brought up the subject of immunopotentiating agents and problems of cancer with fabric and other industrial workers.

Dr. Miller brought up the subject of low-dose radiation. He stated that there are three examples of low-dose radiation having effects on cancer:

(1) Utah Studies
(2) Military personnel who watched nuclear explosion tests;
(3) Nuclear shipyard workers

All of these three groups developed leukemia more often than the normal population. Emphasis in the U.S. has now been directed on research on radiation effects and more funds will be channeled into the basic research in the future.

Dr. Sugimura suggested that careful investigations should be made into the fate of survivors of Hiroshima and Nagasaki, but that these meetings should be kept low-key. He felt that it would not be a good idea to publicize the studies, as it would evoke strong reactions to the atomic bombings and radiation. He also stated that large programs on screening for stomach cancer are on-going.

Dr. Miller stated that with the focus on radiation now, perhaps less importance is being placed on chemical carcinogenesis, which should not be the case.

Dr. Yamamura brought up the studies and use of cytoxin, and the possible role in causing secondary cancers.

Dr. Sugano stated that in Nagasaki there is increased incidence of leukemia, breast cancer and stomach cancer.

Dr. Weinstein suggested that in the future a meeting on prevention would be fruitful.

Dr. Miller mentioned xeroderma pigmentosum, as an example, in which clinical observations in man lead to basic research. Host susceptibility to tumors is a very important subject, which has not been fully investigated.

Dr. Weinstein stated that once you tell people that maybe 80% of cancers are preventable, they will want to know how to prevent them. Physicians will need to know how to interpret data and determine implications. He then asked if chemical dumps posed a problem in Japan also. Dr. Sugimura stated that there were many problems associated with chemical dumps in Japan and that he felt that this area should be explored under the Program.

Dr. Miller stated that the National Academy of Sciences has a committee on chemical disasters, which is studying the problem. Also, that there is some surveillance going on after a PCB accident. Studies are indicating that drugs are metabolized at different rates. Also, the same problems are associated with PBB's.

Dr. Weinstein stated that they are planning a conference on "Biochemical Epidemiology" which would focus on laboratory methodologies, markers, blood metabolism and immunological markers. He stated that a future conference could be planned on chemical-viral interactions.

Dr. Miller closed by stating that this meeting had been very successful, with a variety of thoughts being expressed. He felt that this was due to the flexible structure of the meeting.

He thanked Ms. Takeuchi and Mrs. Day, Dr. Omata, Mr. Soda, Dr. Sugano and all the participants for sharing their valuable time and knowledge.

Dr. Sugano agreed, saying that he was pleased to attend the first meeting of the second five-year Program. He felt that the meeting was extremely successful. He was pleased that the new Chairman of the U.S. side was an old friend, and the Japanese side was pleased to have him involved in the Program in this new capacity.

Mr. Soda expressed the feeling that administrators should serve the Programs by trying to keep the procedural requirements at a minimum.

Dr. Sugano expressed his sincere thanks to Dr. Guy R. Newell, who was Chairman of the Program for the first five years.

The meeting was adjourned at 10:45 A.M., Friday, May 25, 1979.

Respectively submitted,

Robert R. Omata, Ph.D.
Executive Secretary
US-Japan Cooperative
Cancer Research Program
National Cancer Institute

US/Japan Coordinators and Principal Advisors

I. Etiology

Coordinators:

I. Bernard Weinstein Columbia University	Takashi Sugimura National Cancer Center

Advisors:

1. Epidemiology

Robert W. Miller NCI	Takeshi Hirayama National Cancer Center

2. Chemical and Radiation Carcinogenesis

Harry B. Gelboin NCI	Shozo Takayama Japanese Foundation for Cancer Research

3. Viral Carcinogenesis

Hidesaburo Hanafusa Rockefeller University	Hiroto Shimojo University of Tokyo
Thomas Benjamin Harvard University	

4. Genetics

Warren Nichols Institute for Medical Research, Camden, NJ	Susumu Nishimura National Cancer Center

II. Biology and Diagnosis

Coordinators:

William D. Terry NCI	Yuichi Yamamura Osaka University

Advisors:

1. Cellular and Molecular Biology

Ira Pastan NCI	Yoji Ikawa Japanese Foundation for Cancer Research

2. Immunology

Richard Hodes
NCI

Toshiyuki Hamaoka
Osaka University

3. Automated Cytology

Myron Melamed
Memorial Sloan-Kettering
Cancer Center

Yoshio Tenjin
Kyoundo Hospital

III. Treatment

Coordinators:

Stephen K. Carter
Northern California
Cancer Program

Yoshio Sakurai
Japanese Foundation for
Cancer Research

Advisors:

1. Preclinical Drug Development

John Douros
NCI

Abraham Goldin
NCI

1. Breast Cancer

Hiroki Koyama
Center for Adult Diseases
Osaka

2. Chemotherapy

Franco Muggia
NCI

2. Gastric Cancer

Makoto Ogawa
Japanese Foundation for
Cancer Research

3. Immunotherapy

Steven Rosenberg
NCI

3. Lung Cancer

Shoji Hattori
Center for Adult Diseases
Osaka

4. Radiation Oncology

Glenn Sheline
University of California
San Francisco

4. Radiation Oncology

Yoichiro Umegaki
Japanese Foundation for
Cancer Research

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